Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Biosimilars for Rheumatoid Arthritis***
-November 2020-

Background:

Biosimilars are biological products, which are "highly similar" to an FDA-approved licensed biologic product, often referred to as reference or originator products. Biosimilars were introduced in the United States after the Biologics Price Competition and Innovation (BPCI) Act of 2009 was passed as part of the Affordable Care Act.[1] The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed the biosimilars for rheumatoid arthritis (RA) at the November 2020 meeting. This review included 14 biosimilars approved by the Food and Drug Administration (FDA) for adalimumab, etanercept, infliximab, and rituximab. Only 5 biosimilar products are however commercially available as of October 2020 (3 for infliximab and 2 for rituximab, although only one of rituximab biosimilar is currently indicated for RA). Currently, no biosimilar products are named to the National Core Formulary. After review of clinical data, position statements from rheumatologic medical organizations, and agency data on procurement, utilization, and safety, **no modifications were made to the National Core Formulary**.

Discussion:

Due to the rising drug costs and associated healthcare expenditures in the United States, the BPCI Act of 2009 was signed into law in 2010 as part of the Affordable Care Act to improve access to care and reduce drug costs through competition. The BPCI Act created an abbreviated licensure pathway for biological products to demonstrate biosimilarity or interchangeability with FDA-licensed reference products.[1] This licensure pathway permits a biosimilar biologic product to be licensed under 351(k) of the Public Health Service (PHS) Act based on less than a full complement of product-specific preclinical and clinical data. Biosimilar means that a biological product is "highly similar" to the reference product and that there are "no clinically meaningful differences" between the two in terms of safety, purity, and potency "notwithstanding minor differences in clinically inactive components".[1,2] Currently, there are no interchangeable products approved by the FDA. Since the totality of evidence relies on analytical data complemented with animal data and clinical studies to demonstrate biosimilarity, biosimilar products can be approved for one or more conditions of use for which the FDA-licensed reference product is indicated based on extrapolation data.

Select Comparative Trials for infliximab biosimilars

Given the number of commercially available biosimilar products for RA, the NPTC reviewed clinical data for two infliximab biosimilars – Inflectra® (infliximab-dyyb) and Renflexis® (infliximab-abda).

- PLANETAS was a phase I, randomized, double-blind study comparing pharmacokinetics, safety, and efficacy of CT-P13 (later approved as infliximab-dyyb) with originator infliximab in patients with ankylosing spondylitis.[3]
- PLANETRA was a phase III, randomized, double-blind study comparing safety and efficacy of CT-P13 with originator infliximab in patients with RA.[4]
- Choe et al. conducted a phase III, randomized, double-blind study comparing safety and efficacy of SB2 (later approved as infliximab-abda) with originator infliximab in patients with RA.[5]
- Smolen et al. conducted a phase III, randomized, double-blind study assessing efficacy, safety, immunogenicity in patients with RA.[6]
- In summary, all studies concluded that respective biosimilars were comparable with originator infliximab in terms of efficacy, safety, and immunogenicity.

Select Long Term Safety Trials for infliximab biosimilars

- Yoo et al. conducted a phase III, randomized, double-blind study of the safety and efficacy of CT-P13 with originator infliximab up to 54 weeks in patients with RA using the PLANETRA study group.[7]
- Park et al. conducted an open-label extension study using the PLANETAS treatment groups comparing the efficacy and safety data among patients started and maintained on the study drug CT-P13 and those switched to the study drug at week 54. The study evaluated long-term safety data up to 102 weeks.[8]
- Tanaka et al. studied long-term safety and efficacy effects of CT-P13 in Japanese patients with RA up to 134 weeks in patients started and maintained on the study drug and those switched to the study drug at week 54.[9]
- All of these studies found that the safety, efficacy, and immunogenicity were also comparable between the biosimilar and the originator products.

Multiple Switch Studies for etanercept and adalimumab biosimilars

- EGALITY was a phase III, confirmatory study comparing safety, efficacy, and immunogenicity data in patients with plaque-type psoriasis using GP2015 (later approved as etanercept-szzs) and originator etanercept up to 52 weeks. At the conclusion of the study, 178 patients were switched up to three times between the study and the originator drugs

while 274 patients remained on the same therapy. The researchers found that the efficacy, safety, and immunogenicity data were similar between the patients who continued the therapy and those who were switched.[10]

- ADACCESS was a phase III, randomized, double-blind study comparing efficacy, safety, and immunogenicity between GP2017 (later approved as adalimumab-adaz) and originator adalimumab among patients with plaque psoriasis up to 51 weeks. The patients were switched up to 4 times between study and originator drugs. Researchers found no differences in primary end points.

Findings:

Currently, rheumatologic medical organizations including the American College of Rheumatology recommend that clinicians involve patients when considering to start, switch, or stop a biosimilar product. Patients should give informed consent after being counseled on the benefits and risks of biosimilar products. Due to ongoing patent lawsuits, many FDA-approved biosimilar products remain commercially unavailable. With recent, well-designed (albeit limited) trials demonstrating clinical similarity with the reference drug of pre-specified safety and efficacy endpoints, the use of biosimilar products within IHS creates favorable fiscal opportunities that advantage the healthcare system through reduced acquisition costs.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

1. Center for Drug Evaluation and Research. Implementation of the Biologics Price Competition and Innovation Act (BPCIA) of 2009. U.S. Food and Drug Administration. Accessed May 1, 2020.
2. Center for Drug Evaluation and Research. "Biosimilar Development, Review, and Approval." U.S. Food and Drug Administration, FDA.
3. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72(10):1605-1612.
4. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72(10):1613-1620.
5. Choe JY, Prodanovic N, Niebrzydowski J, et al. A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product Remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76(1):58-64.
6. Smolen JS, Choe JY, Prodanovic N, et al. Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. Ann Rheum Dis. 2018;77(2):234-240.
7. Yoo DH, Racewicz A, Brzezicki J, et al. A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther. 2016;18:82. Published 2016 Apr 2.
8. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Annals of the Rheumatic Diseases 2017;76: 346-354.
9. Tanaka Y, Yamanaka H, Takeuchi T, et al. Safety and efficacy of CT-P13 in Japanese patients with rheumatoid arthritis in an extension phase or after switching from infliximab. Mod Rheumatol. 2017;27(2):237-245.
10. Gerdes S, Thaçi D, Griffiths CEM, et al. Multiple switches between GP2015, an etanercept biosimilar, with originator product do not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis: 30-week results from the phase 3, confirmatory EGALITY study. J Eur Acad Dermatol Venereol. 2018;32(3):420-427.
11. Blauvelt A, Lacour JP, Fowler JF Jr, et al. Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches. Br J Dermatol. 2018;179(3):623-631.