INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Adalimumab Biosimilars***
-October 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a comprehensive drug review of adalimumab biosimilar agents. Medication(s) listed on the National Core Formulary (NCF) relevant to this review include the Tumor Necrosis Factor inhibitors (TNFi) adalimumab -or- etanercept, which were originally added to the NCF in May 2016. The NPTC last reviewed the TNFi drug class in January 2023. Following the review and analysis, and in consultation with the IHS National Supply Service Center, the NPTC **tabled any motion(s)** regarding this drug review.

Discussion:

Adalimumab (Humira®), the first fully human monoclonal antibody to inhibit TNF alpha (halting the inflammatory process), was approved in the United States (U.S.) in 2002 for rheumatoid arthritis (RA).[1] It achieved near immediate success due to its substantial reduction of RA symptoms, rapid onset of action, and sustained efficacy and safety, when given alone or in combination with methotrexate.[2] Since its approval, the range of conditions for Humira® use has expanded to include autoimmune, rheumatologic and gastrointestinal diseases. The product insert for Humira® currently lists 9 indications, namely rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, plaque psoriasis, juvenile idiopathic arthritis, ulcerative colitis, hidradenitis suppurative, and uveitis.[3] The combination of safety, effectiveness and approved use in multiple conditions helped Humira® become the highest grossing pharmaceutical in the history of the world, garnering over $200 Billion in sales over two decades.[1,4] Notably, during this time the manufacturer raised the drug cost 27 times, totaling a relative ~470% increase from its original price.[4] Internal pharmacoeconomic data verify that Humira® has been consistently included in the top 5 highest individual drug expenditures in IHS for over a decade.

Biosimilars offer healthcare systems with therapeutically equivalent, lower cost alternatives to the approved reference (originator) products, thereby expanding access to patients with previously unmet needs for these therapies. In the U.S., the safety and clinical integrity of biosimilars is assured through stringent manufacturing practices governed by the FDA. Moreover, the FDA's structured biosimilar approval process provides added confidence to prescribers that these biological agents will offer the same treatment benefits as their reference products.[5] To date, the FDA has approved 43 biosimilars; internationally there have been over 200 biosimilars approved. Adding to this, in the European Union where biosimilar use is more prominent, no biosimilars have been withdrawn for safety reasons and no biosimilar-related adverse events have been added to any biosimilar product inserts.[1] Early recognition of the clinical and economic advantages with biosimilars led the NPTC to review biosimilar products and/or classes in Nov 2016; Nov 2020; Oct 2021, and Oct 2023.

At the time of this writing, the FDA's Purple Book (containing information on all FDA-approved biological products) lists the following 9 approved adalimumab biosimilars. All are commercially available for purchase by I/T/U facilities.

Biosimilar Product (PROPRIETARY)	BLA Number	Strength(s)	Route of Administration	Original Approval Date	Available Forms / Notes
Adalimumab-atto **(AMJEVITA)**	761024	10MG, 20MG, 40MG, 80MG	SC Injection (citrate-free)	September 2016	Autoinjector; Pre-filled Syringe =Launched 1/31/2023=
Adalimumab-adbm **(CYLTEZO)**	761058	10MG, 20MG, 40MG	SC Injection (citrate-free)	August 2017	Autoinjector; Pre-filled Syringe (***INTERCHANGEABLE***)
Adalimumab-adaz **(HYRIMOZ)**	761071	10MG, 20MG, 40MG, 80MG	SC Injection	October 2018	Autoinjector; Pre-filled Syringe
Adalimumab-bwwd **(HADLIMA)**	761059	40MG	SC Injection	July 2019	Autoinjector; Pre-filled Syringe; Single-dose Vial *(Seeking interchangeability)*
Adalimumab-afzb **(ABRILADA)**	761118	10MG, 20MG, 40MG	SC Injection (citrate-free)	November 2019	Autoinjector; Pre-filled Syringe; Single-dose Vial (***INTERCHANGEABLE***)
Adalimumab-fkjp **(HULIO)**	761154	20MG, 40MG	SC Injection (citrate-free)	July 2020	Autoinjector; Pre-filled Syringe *(Seeking interchangeability)*
Adalimumab-aqvh **(YUSIMRY)**	761216	40MG	SC Injection (citrate-free)	December 2021	Autoinjector; Pre-filled Syringe
Adalimumab-aacf **(IDACIO)**	761255	40MG	SC Injection (citrate-free)	December 2022	Autoinjector; Pre-filled Syringe
Adalimumab-aaty **(YUFLYMA)**	761219	40MG	SC Injection (citrate-free)	May 2023	Autoinjector; Pre-filled Syringe *(Seeking interchangeability)*

BLA = Biological Licensure Applications; SC = Subcutaneous

Patent protection for Humira® officially ended in the U.S. in 2016 however, through settlement agreements with biosimilar manufacturers, the commercial availability of adalimumab biosimilars was delayed until January 2023. Interestingly, the patent for Humira® expired in 2018 in Europe, at which point European providers took immediate advantage of the lower cost biosimilars. This resulted in the majority of current, published, real-world data on adalimumab biosimilar use being derived from Europe. The following information was included in the clinical presentation provided to the NPTC and served to guide and support the formulary management decision.

COMPARATIVE LITERATURE:

A 2021 summary review of clinical trials directly compared Humira® to the seven approved adalimumab biosimilars (at that time) for the treatment of RA.[6] Authors reported no statistically significant differences in any primary endpoints, including those for safety (i.e., treatment-emergent adverse events, [TEAE]), efficacy (i.e., American College of Rheumatology composite measure of 20% improvement, [ACR20]) and immunogenicity (i.e., development of anti-drug antibodies). All study patients were naïve to biologics (i.e., no prior use of TNF inhibitors), resulting in the authors concluding that adalimumab biosimilars could safely serve as the initial choice of biologic agent in patients desiring to start TNFi therapy.

A 2023 meta-analysis of seven RCTs (N=2589) compared the safety and efficacy outcomes of adalimumab biosimilars to Humira® in the treatment of plaque psoriasis.[7] After 16 weeks of treatment, no differences in the Psoriasis Area and Severity Index (primary efficacy endpoint) of 50%, 75%, 90% and 100% improvement were noted between comparators (RR 0.99; 95% CI: 0.95-1.03, p=0.65). Safety indicators, including severe adverse events (SAEs), AEs leading to discontinuation, serious infection, TEAE, and AEs of Special Interest, were also reported with no statistically significant differences noted between treatments. Heterogeneity (I^2) indices fluctuated slightly between individual safety indicators but were considered low for all comparisons ($I^2 \leq 36\%$). Findings of aforementioned safety indicators at 51 weeks were also nonsignificant, including withdrawal rates due to AEs (RR 0.67; 95% CI: 0.40-1.13, p=0.13).

A network meta-analysis in 2023 evaluated eight RCTs (N=3577) of Humira® and adalimumab biosimilars in RA patients who had received methotrexate for ≥12 weeks.[8] Pooled data from direct and indirect studies of all adalimumab products were compared for individual product safety and effectiveness. No statistically significant differences were observed in the primary endpoints for safety (SAEs) or efficacy (ACR20 response rates) between adalimumab biosimilars or between Humira® and any adalimumab biosimilar. Findings support that adalimumab biosimilars are safe, effective, well tolerated and pharmacologically comparable to Humira®.

Multiple European real-world studies have evaluated non-medical (i.e., economic) switching from Humira® to adalimumab biosimilars most commonly in patients treated for ankylosing spondyloarthritis, inflammatory bowel disease, psoriasis, or RA. In general, authors consistently concluded that switching to adalimumab biosimilars had no substantial impact on safety, efficacy or immunogenicity; furthermore, reported biosimilar retention rates were generally considered high. Adverse events (mainly injection site reactions) and lack of effect were infrequent but routinely noted as the primary reasons for patient switch-back to Humira®. Collectively, these findings offer healthcare providers with confidence that patients who are transitioned to adalimumab biosimilars will continue to achieve desired treatment outcomes without substantial risk of treatment failure or increased adverse events leading to discontinuation.[9-14]

Findings:

Evidence from multiple RCTs and observational, real-world studies consistently supports that adalimumab biosimilars are safe and effective for patients initiating adalimumab or when switching from Humira®. These therapeutically equivalent adalimumab alternatives have added economic benefit to the IHS and are now commercially available from multiple manufacturers under various proprietary names. When switching patients from Humira® to adalimumab biosimilars, prescribers and pharmacists should assure clear and comprehensive education is provided to patients regarding the therapeutic equivalence of both treatments.

References:

1. Millan-Martin S, et al. Multi-attribute method (MAM) to assess analytical comparability of adalimumab biosimilars. J Phar Bio Anal. 2023;115543.
2. Rau R. Adalimumab in the treatment of active rheumatoid arthritis: the initial results of five trials. Ann Rheum Dis 2002: 61(Suppl II): 70-73.
3. HUMIRA® (adalimumab) injection, for subcutaneous use. Product Insert. North Chicago, IL 60064. AbbVie Inc. 02/2021
4. Gibbons J, et al. Humira: The First $20 Billion Drug. Am J Manag Care. 2023; 29(2):78-80.
5. U.S Food and Drug Administration. Biosimilars: Overview for Health Care Professionals. Accessed Nov 7, 2023.
6. Lu X, et al. Efficacy and safety of adalimumab biosimilars: Current critical clinical data in rheumatoid arthritis. Frontier Immunol. 2021; 12:638444.
7. Li C, et al. Efficacy and safety evaluations of adalimumab biosimilars in the treatment of psoriasis. J Dermatolog Treat. 2023; 34(1): 2249145.
8. Lee YH, Song GG. Comparative efficacy and safety of adalimumab biosimilars and adalimumab in patients with rheumatoid arthritis presenting an insufficient response to methotrexate: a network meat-analysis. Z Rheumatol 2023: 82:64-70.
9. Garcia-Beloso N, et al. Switching between reference adalimumab and biosimilars in chronic immune-mediated inflammatory diseases Br J Clin Pharmacol. 2022; 88:1529-50.
10. Redeker I, et al. Treatment with adalimumab in patients with chronic inflammatory rheumatic diseases. Ther Adv Musculoskel Dis. 2023; 15: 1-12.
11. Muller-Ladner U, et al. The PROPER Study: A 48-week, pan-European, real-world study of biosimilar SB5 following transition from reference adalimumab in patients with immune-mediated inflammatory disease. Biodrugs. 2023; 37(6):873-89.
12. Van adrichem RC, et al. The non-medical switch from reference adalimumab to biosimilar adalimumab is highly successful in a large cohort of patients with stable inflammatory rheumatic joint diseases. Rheumatol Ther. 2022: 9:1109-1118.
13. Casanova MJ, et al. Real-world outcomes of switching from adalimumab originator to adalimumab biosimilar in patients with inflammatory bowel disease: The ADA-SWITCH study. Aliment Pharmacol Ther. 2023; 58:60-70.
14. Lontai L, et al. Non-medical switch from the originator to biosimilar and between biosimilars of adalimumab in inflammatory bowel disease –a prospective, multicentre study. Dig Liver Dis. 2022: 54(12):1639-45.