MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

POLICY:	Ankylosing Spondylitis (AS)	**P&T DATE:**	05/11/2021
CLASS:	Rheumatology/Anti-inflammatory Disorders	**REVIEW HISTORY** (*month/year*)	02/08, 05/10, 02/12, 10/14, 02/16, 02/17, 02/18, 05/19, 05/20
LOB:	Medi-Cal		

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the HPSJ Pharmacy and Therapeutic Advisory Committee.

OVERVIEW

Ankylosing Spondylitis (AS) is an inflammatory condition that usually involves the spine.[1] Unlike rheumatoid arthritis (RA), oral DMARDs (methotrexate, leflunomide, etc) have not been effective in the treatment of AS. NSAIDs (ibuprofen, naproxen, etc) and physical therapy are first-line treatment. In patients who are symptomatic despite NSAID treatment, treatment with TNF biologics are recommended. This review will examine the treatment guidelines of AS, the currently available AS drug products, and their coverage criteria.

Table 1. Available Ankylosing Spondylitis Agents *(Current as of 2/2021)*

Formulary Agents					
Therapeutic Class	**Generic Name (Brand Name)**	**Available Strengths**	**Fml Limits**	**Cost/ Month**	**Notes**
Biologics	Adalimumab (Humira, Humira CF)	20mg/0.4ml, 40mg/0.8ml	PA; PL; SP	$5,523.17	Reserved for treatment failure to 2 NSAIDs tried within the last 30-60 days.
	Etanercept (Enbrel)	50mg/ml, 25mg/ml,	PA; PL; SP	$5,707.17	Reserved for treatment failure to 2 NSAIDs tried within the last 30-60 days.
	Infliximab-dyyb (Inflectra) Infliximab-abda (Renflexis)	100mg IV vial	PA; PL; SP	--	Reserved for treatment failure to 2 NSAIDs tried within the last 30-60 days.
	Infliximab (Remicade)	100mg IV vial	NF	--	Non-Formulary
	Golimumab (Simponi)	50mg/0.5ml, 100mg/ml	PA; PL; SP	$4,905.20	Reserved for treatment failure to either Adalimumab, Etanercept, or Infliximab.
	Certolizumab (Cimzia)	200mg/ml	PA; PL; SP	--	Reserved for treatment failure to either Adalimumab, Etanercept, or Infliximab.
	Secukinumab (Cosentyx)	150mg/ml	PA; PL; SP	$6,509.33	Reserved for treatment failure to either Adalimumab, Etanercept, or Infliximab.
	Ixekizumab (Taltz)	80 mg/ml	PA; PL; SP	$5,389.36	Reserved for treatment failure to either Adalimumab, Etanercept, or Infliximab.

PL = Prescriber Limit, (Must be prescribed by Rheumatologist); PA = Prior Authorization Required; NF = Non-Formulary; SP = Specialty

EVALUATION CRITERIA FOR APPROVAL/EXCEPTION CONSIDERATION

Below are the coverage criteria and required information for each agent. These coverage criteria have been reviewed approved by the HPSJ Pharmacy & Therapeutics (P&T) Advisory Committee. For conditions not covered under this Coverage Policy, HPSJ will make the determination based on Medical Necessity as described in HPSJ Medical Review Guidelines (UM06).

Biologics

1st line—Adalimumab (Humira, Humira CF), Etanercept (Enbrel), Infliximab (Inflectra, Renflexis)

- ❒ **Coverage Criteria:** Reserved for documented symptomatic AS despite treatment with NSAIDs (unless NSAID-intolerant). An adequate trial is defined as at least 2 different NSAIDs tried over 1 month or 2 different NSAIDs over 2 months.
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Prescription history showing at least 2 NSAIDs tried.
- ❒ **Other Notes:** Medication is to be dispensed by HPSJ's designated specialty pharmacy. Must be initiated by a rheumatologist. Biologics exceeding labeled standard maintenance doses may be approved 1 month at a time. Subsequent fills of the increased maintenance dose will require documentation of symptom improvement.
- ❒ **Non Formulary:** Remicade

2nd line—Certolizumab (Cimzia), Golimumab (Simponi), Secukinumab (Cosentyx), Ixekizumab (Taltz)

- ❒ **Coverage Criteria:** Reserved for treatment failure to Adalimumab, Etanercept, or Infliximab.
- ❒ **Limits:** None
- ❒ **Required Information for Approval:** Prescription history showing at least 3 month trial of one first line agent (Adalimumab, Etanercept, or Infliximab).
- ❒ **Other Notes:** Medication is to be dispensed by HPSJ's designated specialty pharmacy. Must be initiated by a rheumatologist. Biologics exceeding labeled standard maintenance doses may be approved 1 month at a time. Subsequent fills of the increased maintenance dose will require documentation of symptom improvement.

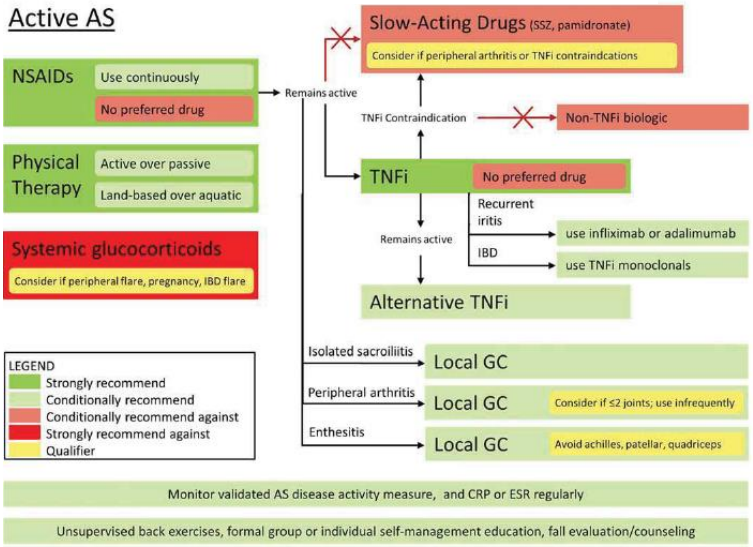
CLINICAL JUSTIFICATION

The goals of treatment are to reduce symptoms to maintain body function and quality of life. The *2015 American College of Rheumatology (ACR)/Spondylitis Association of America (SAA)/Spondyloarthritis Research and Treatment Network (SRTN) Guidelines*[2] recommends the following:

Active AS

- NSAIDs and physical therapy are first-line treatment.
  - The guidelines define "**adequate trial**" as "lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete responses to at least 2 different NSAIDs over 2 months."
- In patients who are symptomatic despite NSAID treatment, treatment with TNF biologics are recommended.
  - There is insufficient evidence to favor one TNF biologic over another. However, experts agreed that in patients with AS and inflammatory bowel disease, infliximab or adalimumab is preferred over etanercept due to lower rates of iritis.
  - For patients with active AS despite treatment with TNF biologic, the guidelines recommend switching to another TNF biologic (as opposed to adding a DMARD).

Figure 1: ACR/SAA/SRTN ctive AS Treatment Algorithm



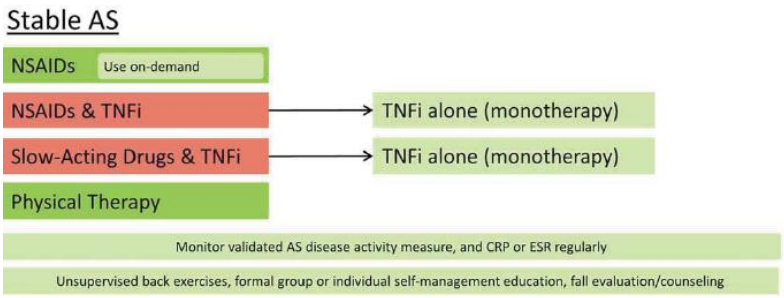
- According to the *2019 ACR/SAA/SRTN Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis* guidelines, the guidelines recommend for the consideration of the use of biological disease-modifying antirheumatic drugs (bDMARDs) in patients with persistently high disease activity despite conventional treatments, with a preference for TNFi therapy over interleukin-17 inhibitors (IL-17i).[28]
- Methotrexate and leflunomide have shown to have minimal benefit and are associated with side effects. The benefits did not outweigh the risks and, therefore, are generally not recommended.
  - Sulfasalazine was shown to have a small benefit on pain relief and may be an option for patients who cannot use TNF biologics.
  - DMARDs are preferred over non-TNF biologics (abatacept, tocilizumab, ustekinumab, etc) due to questionable efficacy and study bias.
- Systemic glucocorticoids are not recommended due to lack of strong safety and efficacy data.

Stable AS

- Patients with stable AS or on stable treatment regimen, experts recommend using NSAIDs on an as-needed basis.
- Patients with stable AS receiving both a TNF biologic and NSAIDs or a TNF biologic with DMARDs, may consider discontinuing the NSAID or DMARD and continuing on the TNF biologic as monotherapy.

The efficacy between TNF biologics do not differ significantly but the cost may vary due to differences in administration frequency (twice monthly vs. weekly vs. monthly, and so forth.) Therefore, HPSJ's order of preference of the biologic therapies are based on the cost-benefit ratio where the first-line biologics are agents associated with the lowest cost-benefit ratio.

Figure 2: ACR/SAA/SRTN Stable AS Treatment Algorithm



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REVIEW & EDIT HISTORY

Document Changes	Reference	Date	P&T Chairman
Creation of Policy	Biological Response Modifiers Review 2-19-08.doc	2/2008	Allen Shek, PharmD
Updated Policy	Biologic Response Modifiers 2010 final.docx	5/2010	Allen Shek, PharmD
Updated Policy	TNF MUE summary 2-21-2012.docx	2/2012	Allen Shek, PharmD
Updated Policy	Psoriatic Arthritis & Ankylosing Spondylitis.docx	10/2014	Jonathan Szkotak, PharmD

Updated Policy	Class Review- Biologics, Apremilast, and Tofacitinib in Inflammatory Joint, Skin, and Bowel Diseases.docx	2/2016	Johnathan Yeh, PharmD
Updated Policy	Class Review- Biologics, Apremilast, and Tofacitinib in Inflammatory Joint, Skin, and Bowel Diseases.docx	02/2017	Johnathan Yeh, PharmD
Updated Policy	HPSJ Coverage Policy – Rheumatology – Ankylosing Spondylitis 2018-02.docx	02/2018	Johnathan,Yeh, PharmD
Updated Policy	HPSJ Coverage Policy – Rheum & Immuno – Ankylosing Spondylitis 2019-05.docx	05/2019	Matthew Garrett, PharmD
Updated Policy	Ankylosing Spondylitis.docx	05/2020	Matthew Garrett, PharmD
Updated Policy	Ankylosing Spondylitis.docx	05/2021	Matthew Garrett, PharmD

Note: All changes are approved by the HPSJ P&T Committee before incorporation into the utilization policy

Appendix:

Switch Studies with Biosimilars launched in the US

Study	Study design	Dosage regimen	Key efficacy outcomes	Immunogenicity	Key safety outcomes	Study conclusions
Yoo et al. PLANETRA study switching extension to week 102	Phase III, open-label, extension study RA patients CT-P13 (n = 302) INX (n = 304) for 54 weeks then CT-P13 maintenance (n = 158) or switch to CT-P13 (n = 144) for up to 102 weeks	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 12.5-25 mg/wk + folic acid 55 mg/wk to week 54 then CT-P13/ MTX/folic acid as above (weeks 64-102)	**ACR20 response rate** CT-P13 maintenance: 71.7% CT-P13 switch: 71.8% (95% CI: -10, 10) **ACR50 response rate** CT-P13 maintenance: 48.0% CT-P13 switch: 51.4% **ACR70 response rate** CT-P13 maintenance: 24.3% CT-P13 switch: 26.1% **Mean improvement in DAS28/CRP** CT-P13 maintenance: -2.40 CT-P13 switch: -2.48 **Good EULAR response (CRP)** CT-P13 maintenance: 40.1% CT-P13 switch: 44.4%	**ADAs at week 78** CT-P13 maintenance: 44.7% CT-P13 switch: 46.2% **ADAs at week 102** CT-P13 maintenance: 40.3% CT-P13 switch: 44.8%	**Overall TEAEs** CT-P13 maintenance: 53.5% CT-P13 switch: 53.8% **TEAEs related to treatment** CT-P13 maintenance: 22.0% CT-P13 switch: 18.9% **Most frequently reported TEAEs related to treatment** **CT-P13 maintenance**: infusion related reaction, latent TB, URTI, LRTI, UTI, bursitis **CT-P13 switch**: infusion-related reaction, latent TB, LRTI, abnormal LFT test, URTI, UTI, urticaria **Serious TEAEs** CT-P13 maintenance: 7.5% CT-P13 switch: 9.1% **Serious TEAEs related to treatment** CT-P13 maintenance: 1.3% CT-P13 switch: 2.8% No deaths	Comparable efficacy and tolerability were observed in patients who switched from INX to CT-P13 for an additional year and in those who had long-term treatment with CT-P13 for 2 years
Tanaka et al. Japanese switching extension study to week 134	Phase I/II open-label, singlearm, multicenter, extension study RA patients CT-P13 (n = 50) INX (n = 51) 54 weeks then CT-P13 maintenance (n = 38) or switch to CT-P13 (n = 33) up to week 134	3 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + MTX 6-16 mg/wk + folic acid 55 mg/wk to week 54 then CT-13/MTX/folic acid as above (weeks 64-104); CT-P13 dose increase allowed to 10 mg/wk	**ACR20 response rate** CT-P13 maintenance: 78.4% CT-P13 switch: 62.5% **ACR50 response rate** CT-P13 maintenance: 70.3% CT-P13 switch: 53.1% **ACR70 response rate** CT-P13 maintenance: 54.1% CT-P13 switch: 40.1% **Mean improvement in DAS28/ESR** CT-P13 maintenance: 3.17 CT-P13 switch: 3.96	**ADAs at week 110** CT-P13 maintenance: 11.8% CT-P13 switch: 21.7% **ADAs at week 134** CT-P13 maintenance: 15.6% CT-P13 switch: 17.4%	**Overall TEAEs** CT-P13 maintenance: 89.5% CT-P13 switch: 87.9% **Most frequently reported TEAEs related to treatment** **CT-P13 maintenance**: nasopharyngitis, URTI inflammation, herpes zoster, rash **CT-P13 switch**: nasopharyngitis, infusion-related reaction and	CT-P13 was well tolerated with persistent efficacy in Japanese patients with RA who maintained treatment after 54 weeks and in patients who switched to CT-P13 after 54 weeks of INX treatment

					Osteoporosis **Serious TEAEs** CT-P13 maintenance: 5.3% CT-P13 switch: 12.1%	
Jorgensen et al. NOR-SWITCH	Phase IV randomized, non-inferiority, double blind study RA, AS, PA, Psoriasis patients stable on INX for 24 weeks, then INX maintenance (n=202) or switch to CT-P13(n=206) for 24 weeks	Dose stayed the same as prior to randomization.	Disease worsening occurred in 53 (26%) patients in the infliximab originator group and in 61 (30%) patients in the CT-P13 group.	INX: 7.1% CT-P13" 7.9%	**Overall AE** INX: 70% CT-P13: 68% **Serious adverse events** INX: 10% CT-P13: 9% AE leading to discontinuation: INX: 4% CT-P13: 3%	CT-P13 was shown to be non-inferior to continued treatment with infliximab according to prespecified non-inferiority margin of 15%.
AS						
Park et al. PLANETAS	Phase I double blind, multicenter, parallel group study CT-P13 (N=125) INX (N = 125)	5 mg/kg IV CT-P13 or INX, weeks 0, 2, 6 then q8wks + continued stable use of glucocorticoids/ NSAIDs allowed	ASAS20 response rate CT-P13: 67.0% INX: 69.4% (95% CI: 0.50, 1.59) ASAS40 response rate CT-P13: 54.7% INX: 49.1% (95% CI: 0.73, 2.15) ASAS partial remission CT-P13: 19.8% INX: 17.6%	ADAs at week 30 CT-P13: 19.5% INX: 23.0%	Overall TEAEs CT-P13: 74.2% INX: 67.2% TEAEs related to treatment CT-P13: 50.0% INX: 51.6%	CT-P13 and INX have highly comparable efficacy, safety and immunogenicity and PK profiles up to week 54