Clinical Policy Title:	etanercept
Policy Number:	RxA.734
Drug(s) Applied:	Enbrel®
Original Policy Date:	04/18/2022
Last Review Date:	04/18/2022
Line of Business Policy Applies to:	All lines of business

Background

Enbrel® is a tumor necrosis factor (TNF) blocker indicated for the treatment of:

- Rheumatoid Arthritis (RA): Enbrel® is indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA). Enbrel® can be initiated in combination with methotrexate (MTX) or used alone.
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older: Enbrel® is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older.
- Psoriatic Arthritis (PsA): Enbrel® is indicated for reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PsA). Enbrel® can be used with or without methotrexate.
- Ankylosing Spondylitis (AS): Enbrel® is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis (AS).
- Plaque Psoriasis (PsO) in patients 4 years or older: Enbrel® is indicated for the treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis (PsO) who are candidates for systemic therapy or phototherapy.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
etanercept (Enbrel®)	Rheumatoid Arthritis	Adult: 50 mg once weekly with or without methotrexate (MTX)	50 mg/week
	Polyarticular Juvenile Idiopathic Arthritis in patients aged 2 years or older	Weight < 63 kg: 0.8 mg/kg subcutaneously once weekly Weight ≥ 63 kg: 50 mg subcutaneously once weekly	50 mg/week
	Psoriatic Arthritis	Adult: 50 mg once weekly with or without methotrexate (MTX)	50 mg/week subcutaneously. Induction therapy for psoriatic arthritis should not exceed 100 mg/week with no more than 50 mg/dose subcutaneously.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
	Ankylosing Spondylitis	50 mg once weekly	50 mg/week
	Plaque Psoriasis in patients 4 years or older	Adult PsO: 50 mg twice weekly for 3 months, followed by 50 mg once weekly Pediatric PsO: Weight < 63 kg: 0.8 mg/kg subcutaneously once weekly Weight ≥ 63 kg: 50 mg subcutaneously once weekly	50 mg/week

Dosage Forms

- Injection: 25 mg/0.5 mL and 50 mg/mL solution in a single-dose prefilled syringe
- Injection: 50 mg/mL solution in single-dose prefilled SureClick® Autoinjector
- Injection: 25 mg/0.5 mL solution in a single-dose vial
- For Injection: 25 mg lyophilized powder in a multiple-dose vial for reconstitution
- Injection: 50 mg/mL solution in Enbrel Mini® single-dose prefilled cartridge for use with the AutoTouch® reusable autoinjector only

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Rheumatoid Arthritis (must meet all):

1. Diagnosis of Rheumatoid Arthritis (RA);
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. Trial and failure of a ≥ 3 months of at least one conventional systemic therapy (methotrexate [MTX], sulfasalazine, leflunomide, hydroxychloroquine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If one biologic DMARD that is FDA-approved for rheumatoid arthritis has been previously tried, then trial of a conventional systemic agent is not required;
5. Members meets both (a and b):
   a. Trial and failure of at least two (2) of the following agents: Humira®, Cimzia®, Rinvoq®, Simponi®/Simponi Aria®, or Xeljanz®/XR unless contraindicated or clinically significant adverse effects are experienced;
      *Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®, Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required.
   b. Trial and failure of both Actemra® and Orencia® unless contraindicated or clinically significant adverse effects are experienced;

6. Dose does not exceed 50 mg/week.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Psoriatic Arthritis (must meet all)**:**
1. Diagnosis of Psoriatic Arthritis (PsA);
2. Prescribed by or in consultation with a dermatologist or a rheumatologist;
3. Age ≥ 18 years;
4. Members meets both (a and b):
   a. Trial and failure of at least two (2) of the following agents: Humira®, Cimzia®, Rinvoq®, Simponi®/Simponi Aria®, Skyrizi®, Stelara®, Tremfya® or Xeljanz®/XR unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®, Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required.
   b. Trial and failure of both Taltz® and Orencia® unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 50 mg/week.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

C. Polyarticular Juvenile Idiopathic Arthritis (must meet all)**:**
1. Diagnosis of Polyarticular Juvenile Idiopathic Arthritis (PJIA);
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 2 years;
4. Trial and failure of a ≥ 3 months trial of at least one (1) conventional systemic therapy (methotrexate [MTX] or leflunomide or sulfasalazine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If one biologic DMARD that is FDA-approved for rheumatoid arthritis has been previously tried, then trial of a conventional systemic agent is not required;
5. Trial and failure of all of the following agents unless contraindicated or clinically significant adverse effects are experienced for all: Humira®, Actemra®, Orencia®, Xeljanz®
6. Dose does not exceed 50 mg/week.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

D. Active Ankolysing Spondylitis (must meet all):
1. Diagnosis of active ankylosing spondylitis (AS);
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. Trial and failure of at least two (2) non-steroidal anti-inflammatory drugs (NSAIDs) at up to maximally indicated doses, each used for at ≥ 4 weeks unless contraindicated or clinically significant adverse effects are experienced;
5. Members meets both (a and b):

a. Trial and failure of at least two (2) of the following agents: Humira®, Cimzia®, Simponi®/Simponi Aria®, unless contraindicated or clinically significant adverse effects are experienced;
*Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®, Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required.
b. Trial and failure of at least one (1) of the following agents: Taltz® or Xeljanz®/XR unless contraindicated or clinically significant adverse effects are experienced;

6. Dose does not exceed 50 mg/week.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

E. Plaque Psoriasis (must meet all)**:**
1. Diagnosis of Plaque Psoriasis (PsO);
2. Age ≥ 4 years;
3. Prescribed by or in consultation with a dermatologist or a rheumatologist;
4. Trial and failure of ≥ 3 months of at least one (1) conventional systemic therapy (methotrexate [MTX], cyclosporin, acitretin) or phototherapy (psoralen plus ultraviolet A light [PUVA]) at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
*Exception: If one biologic DMARD that is FDA-approved for plaque psoriasis has been previously tried, then trial of a conventional systemic agent or phototherapy is not required;
5. Members meets both (a and b):
a. Trial and failure of at least three (3) of the following agents: Humira®, Cimzia®, Skyrizi®, Stelara® or Tremfya® unless contraindicated or clinically significant adverse effects are experienced;
*Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®, Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required.
b. Trial and failure of Taltz® unless contraindicated or clinically significant adverse effects are experienced;
6. Dose does not exceed 50 mg/week.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indications in Section I (must meet all):
1. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 50 mg/week.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
AS: Ankylosing Spondylitis
DMARDs: Disease-Modifying Antirheumatic Drugs
MTX: Methotrexate
nr-axSpA: non-radiographic axial spondyloarthritis

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs
PJIA: Polyarticular Juvenile Idiopathic Arthritis
PsO: Plaque Psoriasis
PsA: Psoriatic Arthritis
RA: Rheumatoid Arthritis
ESR: Erythrocyte Sedimentation Rate
CRP:C-Reactive Protein
PUVA: Psoralen plus ultraviolet A light

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
acitretin	**PsO:** 25 or 50 mg orally once daily	50 mg/day
azathioprine (Azasan®, Imuran®)	**RA:** 1 mg/kg/day orally once daily or divided twice daily	2.5 mg/kg/day
d-penicillamine (Cuprimine®)	**RA (off- label)** Initial dose: 125 or 250 mg orally once daily Maintenance dose: 500 – 750 mg/day orally once daily	1,500 mg/day
cyclosporine (Sandimmune®, Neoral®)	**PsO:** 1 – 4 mg/kg/day orally divided twice daily **RA:** 2.5 – 4 mg/kg/day orally divided twice daily	PsO, RA: 4 mg/kg/day
hydroxychloroquine (Plaquenil®)	**RA (off-label)** Initial dose: 400 – 600 mg/day orally once daily Maintenance dose: 200 – 400 mg/day orally once daily	600 mg/day
leflunomide (Arava®)	**PJIA (off-label)** Weight < 20 kg: 10 mg every other day Weight 20 - 40 kg: 10 mg/day Weight > 40 kg: 20 mg/day **RA:** 100 mg orally once daily for 3 days, then 20 mg orally once daily	PJIA, RA: 20 mg/day
methotrexate	**PsO:** 10 – 25 mg/week orally or 2.5 mg orally every 12 hr for 3 doses/week **PJIA*:** 10 – 20 mg/m^2/week orally, subcutaneous, or intramuscular **RA:** 7.5 mg/week orally, subcutaneous, or intramuscular or 2.5 mg orally every 12 hr for 3 doses/week	30 mg/week

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
NSAIDs (e.g., indomethacin, ibuprofen, naproxen, celecoxib)	**AS, nr-axSpA:** Varies	Varies
Ridaura®	**RA:** 6 mg orally once daily or 3 mg orally twice daily	9 mg/day (3 mg three times daily)
sulfasalazine (Azulfidine®)	**PJIA (off-label):** 30-50 mg/kg/day orally divided twice daily **RA:** 2 g/day orally in divided doses	PJIA: 2 g/day RA: 3 g/day
Biologic DMARDs		
Humira®	**PsO**: Initial dose: 80 mg Maintenance dose: 40 mg subcutaneously every other week starting one week after initial dose **RA**: 40 mg subcutaneously every other week Some patients with RA not receiving concomitant methotrexate may benefit from increasing the frequency to 40 mg every Week or 80 mg every other week **PJIA:** Weight 10 kg (22 lbs) to < 15 kg (33 lbs): 10 mg subcutaneously every other week Weight 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg subcutaneously every other week Weight ≥ 30 kg (66 lbs): 40 mg subcutaneously every other week **AS, PsA**: 40 mg subcutaneously every other week	40 mg every other week 40 mg/week 40 mg every other week 40 mg every other week
Cosentyx®	**PsA:** With loading dose: 150 mg subcutaneous lyat week 0, 1, 2, 3, and 4, followed by 150 mg subcutaneously every 4 weeks Without loading dose: 150 mg subcutaneously every 4 weeks If a patient continues to have active psoriatic arthritis, consider a dosage of 300 mg every 4 weeks. Pediatric Patients 2 years and older: Recommended dosage is administered by subcutaneous injection at weeks 0,1 ,2,3, and 4 and every 4 weeks after:	PsA: 300 mg every 4 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	For patients weighing ≥ 15 kg and < 50 kg the dose is 75 mg. For patients weighing ≥ 50 kg the dose is 150 mg. **AS:** <u>With loading dose:</u> 150 mg subcutaneous at weeks 0, 1, 2, 3, and 4, followed by 150 mg subcutaneous every 4 weeks thereafter <u>Without loading dose:</u> 150 mg subcutaneous every 4 weeks If the patient continues to have active ankylosing spondylitis: 300 mg every 4 weeks can be considered **PsO:** Adults:300 mg subcutaneously at weeks 0, 1, 2, 3, and 4, followed by 300 mg subcutaneously every 4 weeks. (for some patients, a dose of 150 mg may be acceptable) Pediatric Patients 6 years of age and older Weight < 50 kg : 75 mg at weeks 0,1,2,4 and 4 followed by dosing every 4 weeks Weight ≥ 50 kg: 150 mg at weeks 0,1,2,3 and 4 followed by dosing every 4 weeks	AS: 300mg every 4 weeks Adults:300 mg every 4 weeks Pediatrics: Weight < 50 kg: 75 mg every 4 weeks Weight ≥ 50 kg: 150 mg every 4 weeks
infliximab (Remicade®), Renflexis®, Inflectra®, Avsola	**PsA, PsO:** <u>Initial dose:</u> 5 mg/kg intravenous at weeks 0, 2 and 6 <u>Maintenance dose:</u> 5 mg/kg intravenous every 8 weeks **RA:** In conjunction with MTX <u>Initial dose:</u> 3 mg/kg intravenous at weeks 0, 2 and 6 <u>Maintenance dose:</u> 3 mg/kg intravenous every 8 weeks Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks **AS:** <u>Initial dose:</u> 5 mg/kg intravenous at weeks 0, 2 and 6 <u>Maintenance dose:</u> 5 mg/kg intravenous every 6 weeks	PsA, PsO: 5 mg/kg every 8 weeks RA:10 mg/kg every 4 weeks AS: 5 mg/kg every 6 weeks
Simponi Aria®	**AS, PsA RA:** <u>Initial dose:</u> 2 mg/kg IV at weeks 0 and 4 <u>Maintenance dose:</u> 2 mg/kg intravenous every 8 weeks **PJIA:** <u>Initial dose:</u> 80 mg/m^2 at weeks 0 and 4	AS, PsA, RA: 2 mg/kg every 8 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Maintenance dose: 80 mg/m^2 intravenous every 8 weeks	PJIA: 80 mg/m^2 every 8 weeks
Otezla®	**PsO** **PsA:** Initial dose: Day 1: 10 mg orally in morning Day 2: 10 mg orally in morning and 10 mg orally in evening Day 3: 10 mg orally in morning and 20 mg orally in evening Day 4: 20 mg orally in morning and 20 mg orally in evening Day 5: 20 mg orall in morning and 30 mg orally in evening Maintenance dose: Day 6 and thereafter: 30 mg orally twice daily	60 mg/day
Xeljanz® / Xeljanz® oral Solution, Xeljanz® XR	Xeljanz®: **PsA, RA AS**: 5 mg orally twice daily PsA: use in combination with nonbiologic disease-modifying antirheumatic drugs RA: monotherapy or use in combination with nonbiologic disease-modifying antirheumatic drugs Xeljanz® / Xeljanz® oral Solution: **PJIA**: 5 mg twice daily or weight-based equivalent twice daily: • 10 kg ≤ body weight <20 kg: 3.2 mg (3.2 mL oral solution) twice daily • 20 kg ≤ body weight <40 kg: 4 mg (4 mL oral solution) twice daily Body weight ≥40 kg: 5 mg (one 5 mg tablet or 5 mL oral solution) twice daily Xeljanz® XR: **PsA, RA, AS**: 11 mg orally once daily	Xeljanz®: PsA, RA, AS: 10 mg/day Xeljanz® / Xeljanz® oral Solution: 5 mg or 5 ml twice daily Xeljanz® XR: 11 mg/day
Kevzara®	**RA:** 200 mg subcutaneous once every two weeks	200 mg/2 Weeks
Orencia®	**RA, PsA:** Intravenous: weight-based dose at weeks 0, 2, and 4, followed by every 4 weeks Weight < 60 kg: 500 mg per dose Weight 60 to 100 kg: 750 mg per dose Weight > 100 kg: 1,000 mg per dose Subcutaneous: 125 mg once weekly **RA and PsA:** Patients switching from intravenous use to subcutaneous use, administer first subcutaneous dose instead of next scheduled intravenous dose. (For RA: Prior to the first subcutaneous dose, may administer an optional loading dose as a single intravenous infusion as per body weight categories above.)	**RA, PsA:** Intravenous: 1,000 mg every 4 weeks Subcutaneous: 125 mg/week **PJIA:** Intravenous: 1,000 mg every 4 weeks Subcutaneous: 125 mg/week

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	For PsA: Intravenous loading dose is not recommended. **PJIA:** Intravenous: in pediatric patients ≥ 6 years old weight-based dose at weeks 0, 2, and 4, followed by every 4 weeks Weight < 75 kg: 10 mg/kg per dose Weight 75 to 100 kg: 750 mg per dose Weight >100 kg: 1,000 mg per dose. Subcutaneous: In pediatric patients ≥ 2 years old weight-based dose once weekly Weight 10 to < 25 kg: 50 mg per dose Weight 25 to < 50 kg: 87.5 mg per dose Weight ≥ 50 kg: 125 mg per dose	
Kineret®	**RA:** 100 mg subcutaneous once daily	100 mg/day
Olumiant®	**RA:** 2 mg orally once daily	2 mg/day
Siliq®	**PsO:** Initial dose: 210 mg subcutaneous at weeks 0, 1, and 2 Maintenance dose: 210 mg subcutaneous every 2 weeks	210 mg every 2 weeks
Cimzia®	**RA, PsA, AS, nr-axSpA:** Initial dose: 400 mg subcutaneous at 0, 2, and 4 weeks. Maintenance dose: 200 mg subcutaneous every other week (or 400 mg subcutaneous every 4 weeks) **PsO:** 400 mg subcutaneous every other week. For some patients (with body weight ≤ 90 kg), a dose of 400 mg subcutaneous at 0, 2 and 4 weeks, followed by 200 mg subcutaneous every other week may be considered.	**RA, PsA, AS, nr-axSpA:** 400 mg every 4 weeks **PsO:** 400 mg every other week
Simponi®	**AS, PsA, RA:** 50 mg subcutaneous once monthly	50 mg/month
Tremfya®	**PsO, PsA:** Initial dose: 100 mg subcutaneous at weeks 0 and 4 Maintenance dose: 100 mg subcutaneous every 8 weeks Can be used alone or in combination with conventional DMARD e.g., methotrexate	100 mg every 8 weeks
Taltz®	**PsO:** Adult Plaque Psoriasis: Recommended dose is 160 mg subcutaneously (two 80 mg injections) at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks Pediatric Plaque Psoriasis(age 6 years or older): For patients weighing greater than 50 kg:160 mg subcutaneously (two 80 mg injections) at Week 0, followed by 80 mg every 4 weeks. For patients weighing 25-50 kg: 80 mg subcutaneoulsy at Week 0,	**PsO:** 80 mg every 4 weeks **nraxSpA, PsA, AS:** 80 mg every 4 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	followed by 40 mg every 4 weeks. For patients weighing less than 25 kg:40 mg subcutaneously at Week 0, followed by 20 mg every 4 weeks **PsA, AS:** Initial dose: 160 mg (two 80 mg injections) subcutaneous Maintenance dose: 80 mg subcutaneous every 4 weeks.	
Skyrizi®	**PsO:** 150 mg subcutaneous at weeks 0, 4, and every 12 weeks thereafter	150 mg/12 Weeks
Ilumy®	**PsO:** Initial dose: 100 mg subcutaneous at weeks 0 and 4 Maintenance dose: 100 mg subcutaneous every 12 weeks Tildrakizumab should only be administered by a healthcare professional.	100 mg every 12 weeks
Actemra®	**RA:** Intravenous: 4 mg/kg every 4 weeks followed by an increase to 8 mg/kg every 4 weeks based on clinical response. Subcutaneous: Weight < 100 kg: 162 mg every other week, followed by an increase to every week based on clinical response. Weight ≥ 100 kg: 162 mg every week. **PJIA:** Weight < 30 kg: 10 mg/kg intravenously every 4 weeks or 162 mg subcutaneously every 3 weeks. Weight ≥ 30 kg: 8 mg/kg intravenously every 4 weeks or 162 mg subcutaneously every 2 weeks.	**RA**: Intravenous: 800 mg every 4 weeks Subcutaneous: 162 mg every week **PJIA:** Intravenous: 10 mg/kg every 4 weeks Subcutaneous: 162 mg every 2 weeks
Rinvoq®	**RA, PsA:** 15 mg orally once daily Can be used as monotherapy or in combination with methotrexate or other non biologic DMARDs. *For use in adults who have had an inadequate response or intolerance to one or more TNF blockers	15 mg/day
Stelara®	**PsO:** Weight based dosing subcutaneous at weeks 0 and 4, followed by maintenance dose every 12 weeks Adult: Weight ≤ 100 kg: 45 mg (some patients may require doses of 90 mg or maintenance dosing of every 8 weeks) Weight > 100 kg: 90 mg (some patients may require maintenance dosing of every 8 weeks) Pediatrics (Age 6 years and older): Weight < 60 kg: 0.75 mg/kg Weight ≥ 60 to ≤100 kg: 45 mg Weight > 100kg: 90 mg	**PsO:** 90 mg every 8 weeks **PsA:** 45 mg every 12 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	PsA: 45 mg subcutaneous at weeks 0 and 4, followed by 45 mg every 12 weeks	

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Sepsis

  *Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- Boxed Warning(s):
  - Serious infections;
  - Malignancies

APPENDIX D: General Information

- Safety:
  - These agents are immunosuppressives and have the potential to increase the risk of infection and reactivate latent, chronic infections. They should not be administered to patients with a clinically important infection. Caution should be used in patients with chronic infections or history of recurrent infection. If patient develops a serious infection these agents should be discontinued.
  - Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-blocking agent, etanercept, with no added benefit compared to etanercept alone. Because of the nature of the adverse reactions with this combination therapy, similar toxicities may also result from combination of anakinra and other TNF blocking agents.
- Rheumatoid Arthritis:
  - Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics, administered with or without methotrexate, equally positioned as a recommended therapy following a trial of a conventional synthetic disease-modifying antirheumatic drug (DMARD) [e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine].
- Ankylosing Spondylitis:
  - Several AS treatment guidelines recommend a trial of 2 or 3 NSAIDs prior to use of an anti- TNF agent. A two-year trial showed that continuous NSAID use reduced radiographic progression of AS versus on demand use of NSAID.
- Polyarticular Juvenile Idiopathic Arthritis:
  - Failure of MTX in PJIA is defined as disease activity remaining moderate to high despite treatment with MTX.
  - In PJIA, response to treatment is reflected by improvement of disease activity level and poor prognostic features including: reduction in the number of active joints, ESR or CRP, Physician global assessment, patient/parent global assessment, arthritis of the hip or cervical spine, positive RF or ACPA, radiographic damage.
- Psoriatic Arthritis:

- According to the 2019 American College of Rheumatology) TNF inhibitors is recommended over other biologics for use in treatment-naïve patients with psoriatic arthritis, and in those who were previously treated with an oral therapy.

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Review/Revision History	Review/Revision Date	P&T Approval Date
RxA.592.Bilogic_DMARDs was last reviewed and updated on 01/05/2022 and archived on 04/18/2022. For details, please refer to RxA.592.Bilogics_DMARDs.	01/05/2022	04/18/2022
Drug specific policy for Enbrel® was created based on RxA.592.Biologic_DMARDs: 1. Initial Approval Criteria, 1.A.5: Updated to remove prior trial and failure criteria Failure of two (2) of the following: Humira®, Cimzia®, Inflectra®, Renflexis™, Simponi®, Simponi Aria®, and Taltz®; each used for ≥ 3 months, unless contraindicated or clinically significant adverse effects are experienced. 2. Initial Approval Criteria, 1.A.5: Updated to include new trial and failure criteria Members meets both (a and b): a. Trial and failure of at least two (2) of the following agents: Humira®, Cimzia®, Rinvoq®, Simponi®/Simponi Aria®, or Xeljanz®/XR unless contraindicated or clinically significant adverse effects are experienced; *Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®, Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required. b. Trial and failure of both Actemra® and Orencia® unless contraindicated or clinically significant adverse effects are experienced. 3. Initial Approval Criteria, 1.B.4: Updated to remove prior trial and failure criteria Failure of a trial of at least two (2) of the followings, each used for ≥ 3 months, unless contraindicated or clinically significant	02/09/2022	04/18/2022

adverse effects are experienced: Cimzia®, Humira®, Inflectra®, Otezla®, Renflexis®, Rinvoq®, Simponi®, Simponi Aria®, Stelara®, Taltz®, or Xeljanz®/ Xeljanz XR®.

4. Initial Approval Criteria, 1.B.4: Updated to include new trial and failure criteria Members meets both (a and b):
   a. Trial and failure of at least two (2) of the following agents: Humira®, Cimzia®, Rinvoq®, Simponi®/Simponi Aria®, Skyrizi®, Stelara®, Tremfya® or Xeljanz®/XR unless contraindicated or clinically significant adverse effects are experienced;
      *Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®, Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required.
   b. Trial and failure of both Taltz® and Orencia® unless contraindicated or clinically significant adverse effects are experienced.
5. Initial Approval Criteria, 1.C.4: Updated to remove prior trial and failure criteria Failure of a trial of ≥ 3 months of MTX at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced.
6. Initial Approval Criteria, 1.C.4: Updated to include new trial and failure criteria Trial and failure of a ≥ 3 months trial of at least one (1) conventional systemic therapy (methotrexate [MTX] or leflunomide or sulfasalazine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   *Exception: If one biologic DMARD that is FDA-approved for rheumatoid arthritis has been previously tried, then trial of a conventional systemic agent is not required.
7. Initial Approval Criteria, 1.C.5: Updated to remove prior trial and failure criteria Failure of at least two (2) of the followings, each used for ≥ 3 months, unless contraindicated or clinically significant adverse effects are experienced: Humira®, Simponi Aria®, or Xeljanz®/ Xeljanz XR®.
8. Initial Approval Criteria, 1.C.5: Updated to include new trial and failure criteria Trial and failure of all of the following agents unless contraindicated or clinically

significant adverse effects are experienced for all: Humira®, Actemra®, Orencia®, Xeljanz®. 9. Initial Approval Criteria, 1.D.5: Updated to remove prior trial and failure criteria Failure of two (2) of the following: Humira®, Cimzia®, Inflectra®, Renflexis®, Simponi®, Simponi Aria®, Xeljanz®, Xeljanz® XR and Taltz®; each used for ≥ 3 months, unless contraindicated or clinically significant adverse effects are experienced. 10. Initial Approval Criteria, 1.D.5: Updated to include new trial and failure criteria Members meets both (a and b): a. Trial and failure of at least two (2) of the following agents: Humira®, Cimzia®, Simponi®/Simponi Aria®, unless contraindicated or clinically significant adverse effects are experienced; Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®, Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required. b. Trial and failure of at least one (1) of the following agents: Taltz® or Xeljanz®/XR unless contraindicated or clinically significant adverse effects are experienced; 11. Initial Approval Criteria, 1.E.4: Updated trial and failure criteria to rephrase and include phototherapy (psoralen plus ultraviolet A light [PUVA]). 12. Initial Approval Criteria, 1.E.5: Updated to remove prior trial and failure criteria Failure of two of the following, each used for ≥ 3 months, unless contraindicated or clinically significant adverse effects are experienced: Cimzia®, Humira®, Inflectra®, Otezla®, Renflexis®, Skyrizi®, Stelara®, Taltz®. 13. Initial Approval Criteria, 1.E.5: Updated to include new trial and failure criteria Members meets both (a and b): a. Trial and failure of at least three (3) of the following agents: Humira®, Cimzia®, Skyrizi®, Stelara® or Tremfya® unless contraindicated or clinically significant adverse effects are experienced; *Exception: If a total of two TNF inhibitors (Humira®, Cimzia®, Simponi®, Simponi Aria®, Enbrel®) has previously been tried and failed, trial of a third TNF inhibitor is not required.		

b. Trial and failure of Taltz® unless contraindicated or clinically significant adverse effects are experienced; 14. Appendix A: Updated to include abbreviations ESR, CRP and PUVA. 15. Appendix B, Drug Name: Updated to remove discontinued brand-name therapeutic alternative Soriatane®. 16. Appendix B, Drug Name: Updated to include brand-name therapeutic alternative of other biological DMARDs. 17. Disclaimer about contraindications "Contraindications listed reflect statements made in the manufacturer's package insert..." was added to Appendix C. 18. Appendix D, General Information: a. Updated information available from definition of failure of MTX or DMARDs to Guidelines from the American College of Rheumatology (ACR) [2015] have TNF inhibitors and non-TNF biologics. b. Updated to remove Off-label indications for Enbrel®. c. Updated to include Psoriatic Arthritis guidelines from the 2019 American College of Rheumatology, TNF inhibitors is recommended over other biologics. 19. References were reviewed and updated.		