Clinical Policy: Etanercept (Enbrel)

Reference Number: LA.PHAR.250
Effective Date:
Last Review Date: 06.21 Coding Implications
Line of Business: Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Etanercept (Enbrel®) is a tumor necrosis factor (TNF) blocker.

FDA Approved Indication(s)

Enbrel is indicated for the treatment of:

- 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.
- For reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients ages 2 and older
- 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.
- For reducing signs and symptoms in patients with active ankylosing spondylitis (AS)
- 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

Policy/Criteria

Prior authorization is required. Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of Louisiana Healthcare Connections that Enbrel is medically necessary when the following criteria are met:

I. Initial Approval Criteria

A. Ankylosing Spondylitis (must meet all):

1. Diagnosis of AS;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 18 years;
4. Failure of at least TWO non-steroidal anti-inflammatory drugs (NSAIDs) at up to maximally indicated doses, each used for ≥ 4 weeks unless contraindicated or clinically significant adverse effects are experienced;
5. Dose does not exceed 50 mg every week.

Approval duration: 6 months

B. Plaque Psoriasis (must meet all):
1. Diagnosis of moderate-to-severe PsO as evidenced by involvement of one of the following (a or b):
   a. ≥ 3% of total body surface area;
   b. Hands, feet, scalp, face, or genital area;
2. Prescribed by or in consultation with a dermatologist or rheumatologist;
3. Age ≥ 4 years;
4. Member meets one of the following (a or b):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses;
   b. Member has intolerance or contraindication to MTX (*see Appendix D*), and failure of a ≥ 3 consecutive month trial of cyclosporine or acitretin at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated;
5. Dose does not exceed one of the following (a or b):
   a. Adults: 50 mg twice weekly for 3 months, followed by maintenance dose of 50 mg every week;
   b. Pediatrics (*see Appendix E for dose rounding guidelines*) (i or ii):
      i. Weight < 63 kg: 0.8 mg/kg every week;
      ii. Weight ≥ 63 kg: 50 mg every week.

Approval duration: 6 months

C. Polyarticular Juvenile Idiopathic Arthritis (must meet all):
1. Diagnosis of PJIA as evidenced by ≥ 5 joints with active arthritis;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 2 years;
4. Documented baseline 10-joint clinical juvenile arthritis disease activity score (cJADAS-10) (*see Appendix I*)
5. Member meets one of the following (a, b, c, or d):
   a. Failure of a ≥ 3 consecutive month trial of MTX at up to maximally indicated doses;
   b. Member has intolerance or contraindication to MTX (*see Appendix D*), and failure of a ≥ 3 consecutive month trial of leflunomide or sulfasalazine at up to maximally indicated doses, unless clinically significant adverse effects are experienced or both are contraindicated;
   c. For sacroiliitis/axial spine involvement (i.e., spine, hip), failure of a ≥ 4 week trial of an NSAID at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
   d. Documented presence of high disease activity as evidenced by a cJADAS-10 > 8.5 (*see Appendix I*);
6. Dose does not exceed one of the following (a or b):
   a. Adults: 50 mg every week;
   b. Pediatrics (*see Appendix E for dose rounding guidelines*) (i or ii):
      i. Weight < 63 kg: 0.8 mg/kg every week;
      ii. Weight ≥ 63 kg: 50 mg every week.

Approval duration: 6 months

D. Psoriatic Arthritis (must meet all):
1. **Diagnosis of PsA;**
2. **Prescribed by or in consultation with a dermatologist or rheumatologist;**
3. **Age ≥ 18 years;**
4. **Dose does not exceed 50 mg every week.**

Approval duration: 6 months

E. Rheumatoid Arthritis (must meet all):
1. **Diagnosis of RA per American College of Rheumatology (ACR) criteria (*see Appendix F*);**
2. **Prescribed by or in consultation with a rheumatologist;**
3. **Age ≥ 18 years;**
4. **Member meets one of the following (a or b):**
   a. **Failure of a ≥ 3 consecutive month trial of methotrexate (MTX) at up to maximally indicated doses;**
   b. **Member has intolerance or contraindication to MTX (*see Appendix D*), and failure of a ≥ 3 consecutive month trial of at least ONE conventional disease-modifying anti-rheumatic drug [DMARD] (e.g., sulfasalazine, leflunomide, hydroxychloroquine) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;**
5. **Documentation of one of the following baseline assessment scores (a or b):**
   a. Clinical disease activity index (CDAI) score (*see Appendix G*);
   b. Routine assessment of patient index data 3 (RAPID3) score (*see Appendix H*);
6. **Dose does not exceed 50 mg every week.**

Approval duration: 6 months

F. Other diagnoses/indications
1. **Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid.**

II. Continued Therapy

A. All Indications in Section I (must meet all):
1. **Currently receiving medication via Louisiana Healthcare Connections benefit or member has previously met initial approval criteria;**
2. **Member meets one of the following (a, b, or c):**
   a. For RA: member is responding positively to therapy as evidenced by one of the following (i or ii):
      i. A decrease in CDAI (*see Appendix G*) or RAPID3 (*see Appendix H*) score from baseline;
      ii. Medical justification stating inability to conduct CDAI re-assessment, and submission of RAPID3 score associated with disease severity that is similar to initial CDAI assessment or improved;

b. **For pJIA, member is responding positively to therapy as evidenced by a decrease in cJADAS-10 from baseline (*see Appendix I*)**
c. **For all other indications: member is responding positively to therapy;**

3. **If request is for a dose increase, new dose does not exceed 50 mg every week.**

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2):

1. **Currently receiving medication via Louisiana Healthcare Connections benefit and documentation supports positive response to therapy.**
   Approval duration: Duration of request or 6 months (whichever is less); or
2. **Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): :LA.PMN.53 for Medicaid.**

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy –LA.PMN.53 for Medicaid or evidence of coverage documents;

B. Combination use of biological disease-modifying antirheumatic drugs (bDMARDs), including any tumor necrosis factor (TNF) antagonists [Cimzia®, Enbrel®, Simponi®, Avsola™, Inflectra™, Remicade®, Renflexis™], interleukin agents [Arcalyst® (IL-1 blocker), Ilaris® (IL-1 blocker), Kineret® (IL-1RA), Actemra® (IL-6RA), Kevzara® (IL-6RA), Stelara® (IL-12/23 inhibitor), Cosentyx® (IL-17A inhibitor), Taltz® (IL-17A inhibitor), Siliq™ (IL-17RA), Ilumya™ (IL-23 inhibitor), Skyrizi™ (IL-23 inhibitor), Tremfya® (IL-23 inhibitor)], janus kinase inhibitors (JAKi) [Xeljanz®/Xeljanz® XR, Rinvoq™], anti-CD20 monoclonal antibodies [Rituxan®, Riabni™, Ruxience™, Truxima®, and Rituxan Hycela®], selective co-stimulation modulators [Orencia®], or integrin receptor antagonists [Entyvio®] because of the possibility of increased immunosuppression, neutropenia and increased risk of infection.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AS: ankylosing spondylitis
CDAI: clinical disease activity index
cJADAS: clinical juvenile arthritis disease activity score
DMARD: disease-modifying anti rheumatic drug
FDA: Food and Drug Administration
GI: gastrointestinal
MTX: methotrexate
NSAID: non-steroidal anti-inflammatory drug
PsO: plaque psoriasis
PJIA: polyarticular juvenile idiopathic arthritis
PsA: psoriatic arthritis
RA: rheumatoid arthritis
RAPDI3: routine assessment of patient index data 3
TNF: tumor necrosis factor

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
acitretin (Soriatane®)	PsO 25 or 50 mg PO QD	50 mg/day
azathioprine (Azasan®, Imuran®)	RA 1 mg/kg/day PO QD or divided BID	2.5 mg/kg/day
Cuprimine® (d-penicillamine)	RA* Initial dose: 125 or 250 mg PO QD Maintenance dose: 500 – 750 mg/day PO QD	1,500 mg/day
cyclosporine (Sandimmune®, Neoral®)	PsO 2.5 mg/kg/day PO divided BID RA 2.5 – 4 mg/kg/day PO divided BID	4 mg/kg/day
hydroxychloroquine (Plaquenil®)	RA* Initial dose: 400 – 600 mg/day PO QD Maintenance dose: 200 – 400 mg/day PO QD	600 mg/day
leflunomide (Arava®)	PJIA* Weight < 20 kg: 10 mg every other day Weight 20 - 40 kg: 10 mg/day Weight > 40 kg: 20 mg/day RA 100 mg PO QD for 3 days, then 20 mg PO QD	20 mg/day
methotrexate (Rheumatrex®)	PsO 10 – 25 mg/week PO or 2.5 mg PO Q12 hr for 3 doses/week PJIA* 10 – 20 mg/m^2/week PO, SC, or IM RA 7.5 mg/week PO, SC, or IM or 2.5 mg PO Q12 hr for 3 doses/week	30 mg/week
NSAIDs (e.g., indomethacin,	AS Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
ibuprofen, naproxen, celecoxib)		
Ridaura® (auranofin)	RA 6 mg PO QD or 3 mg PO BID	9 mg/day (3 mg TID)
sulfasalazine (Azulfidine®)	PJIA* 30-50 mg/kg/day PO divided BID RA 2 g/day PO in divided doses	PJIA: 2 g/day RA: 3 g/day

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

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): patients with sepsis
- Boxed warning(s):
  - Serious infections
  - Malignancies

Appendix D: General Information

- Definition of failure of MTX or DMARDs
  - Child-bearing age is not considered a contraindication for use of MTX. Each drug has risks in pregnancy. An educated patient and family planning would allow use of MTX in patients who have no intention of immediate pregnancy.
  - Social use of alcohol is not considered a contraindication for use of MTX. MTX may only be contraindicated if patients choose to drink over 14 units of alcohol per week. However, excessive alcohol drinking can lead to worsening of the condition, so patients who are serious about clinical response to therapy should refrain from excessive alcohol consumption.
- Examples of positive response to therapy may include, but are not limited to:
  - Reduction in joint pain/swelling/tenderness
  - Improvement in ESR/CRP levels
  - Improvements in activities of daily living
- Hidradenitis suppurativa:
  - HS is sometimes referred to as: "acne inversa, acne conglobata, apocrine acne, apocrinitis, Fox-den disease, hidradenitis axillaris, HS, pyodermia sinifica fistulans, Velpeau's disease, and Verneuil's disease."
  - Per the 2019 North American guidelines for HS, the limited available evidence does not support use of etanercept for HS. One randomized, double-blind, placebo-controlled study (n = 20) demonstrated no statistically significant improvement in patient or physician-reported outcomes. Other studies

demonstrated either mixed evidence or the limited efficacy was determined using incompletely validated outcome measures.

Appendix E: Dose Rounding Guidelines for PJIA and Pediatric PsO

Weight-based Dose Range	Vial Quantity Recommendation
≤ 25.99 mg	1 vial of 25 mg/0.5 mL
26 to 52.49 mg	1 vial of 50 mg/mL

Appendix F: The 2010 ACR Classification Criteria for RA

Add score of categories A through D; a score of ≥ 6 out of 10 is needed for classification of a patient as having definite RA.

A	Joint involvement	Score
	1 large joint	0
	2-10 large joints	1
	1-3 small joints (with or without involvement of large joints)	2
	4-10 small joints (with or without involvement of large joints)	3
	> 10 joints (at least one small joint)	5
B	Serology (at least one test result is needed for classification)	
	Negative rheumatoid factor (RF) *and* negative anti-citrullinated protein antibody (ACPA)	0
	Low positive RF *or* low positive ACPA * *Low: < 3 x upper limit of normal*	2
	High positive RF *or* high positive ACPA * *High: ≥ 3 x upper limit of normal*	3
C	Acute phase reactants (at least one test result is needed for classification)	
	Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0
	Abnormal CRP or abnormal ESR	1
D	Duration of symptoms	
	< 6 weeks	0
	≥ 6 weeks	1

Appendix G: Clinical Disease Activity Index (CDAI) Score

The Clinical Disease Activity Index (CDAI) is a composite index for assessing disease activity in RA. CDAI is based on the simple summation of the count of swollen/tender joint count of 28 joints along with patient and physician global assessment on VAS (0–10 cm) Scale for estimating disease activity. The CDAI score ranges from 0 to 76.

CDAI Score	Disease state interpretation
≤ 2.8	Remission
> 2.8 to ≤ 10	Low disease activity
> 10 to ≤ 22	Moderate disease activity
> 22	High disease activity

Appendix H: Routine Assessment of Patient Index Data 3 (RAPID3) Score

The Routine Assessment of Patient Index Data 3 (RAPID3) is a pooled index of the three patient-reported ACR core data set measures: function, pain, and patient global estimate of status. Each of the individual measures is scored 0 – 10, and the maximum achievable score is 30.

RAPID3 Score	Disease state interpretation
≤ 3	Remission
3.1 to 6	Low disease activity
6.1 to 12	Moderate disease activity
> 12	High disease activity

Appendix I: Clinical Juvenile Arthritis Disease Activity Score based on 10 joints (cJADAS-10)

The cJADAS10 is a continuous disease activity score specific to JIA and consisting of the following three parameters totaling a maximum of 30 points:

- **Physician's global assessment of disease activity measured on a 0-10 visual analog scale (VAS), where 0 = no activity and 10 = maximum activity;**
- **Parent global assessment of well-being measured on a 0-10 VAS, where 0 = very well and 10 = very poor;**
- **Count of joints with active disease to a maximum count of 10 active joints***

***ACR definition of active joint: presence of swelling (not due to currently inactive synovitis or to bony enlargement) or, if swelling is not present, limitation of motion accompanied by pain, tenderness, or both**

cJADAS-10	Disease state interpretation
≤ 1	Inactive disease
1.1 to 2.5	Low disease activity
2.51 to 8.5	Moderate disease activity
> 8.5	High disease activity

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
RA PsA	25 mg SC twice weekly or 50 mg SC once weekly	50 mg/week
AS	50 mg SC once weekly	50 mg/week
PJIA	Weight < 63 kg: 0.8 mg/kg SC once weekly Weight ≥ 63 kg: 50 mg SC once weekly	50 mg/week
PsO	*Adults:* Initial dose: 50 mg SC twice weekly for 3 months Maintenance dose: 50 mg SC once weekly *Pediatrics:* Weight < 63 kg: 0.8 mg/kg SC once weekly Weight ≥ 63 kg: 50 mg SC once weekly	50 mg/week

VI. Product Availability

- **Single-dose prefilled syringe: 25 mg/0.5 mL, 50 mg/mL**
- **Single-dose prefilled SureClick® autoinjector: 50 mg/ml**
- **Single-dose vial: 25 mg/0.5 mL**
- **Multi-dose vial for reconstitution: 25 mg**
- **Enbrel Mini™ single-dose prefilled cartridge for use with AutoTouch™ reusable autoinjector: 50 mg/mL**

VII. References

1. **Enbrel Prescribing Information. Thousand Oaks, CA: Immunex Corporation: August 2020. Available at https://www.enbrel.com/. Accessed January 20, 2021.**
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6. **Braun J, van den berg R, et al. 2010 Update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Am Rheu Dis*. 2011: 70; 896-904.**
7. **Menter A, Korman NJ, Elmets CA, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 6: Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions. *J Am Acad Dermatol*. 2011;65(1):137-174.**
8. **Beukelman T, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care & Research*. 2011;63(4):465-482.**
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10. **Ringold, S, Weiss PF, et al. 2013 Update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis. *Arthritis Care Res*. 2013; 65 (10): 2499-2512.**

11. **Smolen JS, Landewé R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis*. 2014; 73: 492-509.**
12. **Gossec L, Smolen JS, Ramiro S, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis.* 2015;0:1-12. doi:10.1136/annrheumdis-2015-208337**
13. **Ward MM, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network 2015 recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. *Arthritis & Rheumatology*. 2015. DOI 10.1002/ART.39298.**
14. **Alikhan A, Sayed C, Alavi A, et al. North American Clinical Management Guidelines for Hidradenitis Suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations. Part II: topical, intralesional, and systemic medical management. *J Am Acad Dermatol.* 2019; pii: S0190-9622(19)30368-8. doi: 10.1016/j.jaad.2019.02.068.**
15. **Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol*. 2019;80:1029-72. doi:10.1016/j.aad.201811.057.**
16. **Singh JA, Guyatt G, Ogdie A, et al. 2018 American College of Rheumatology/National Psoriasis Foundation Guideline for the treatment of psoriatic arthritis. *American College of Rheumatology*. 2019; 71(1):5-32. doi: 10.1002/art.40726**

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J1438	Injection, etanercept, 25 mg (code may be used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)

Reviews, Revisions, and Approvals	Date
Converted corporate to local policy	06.2021

Reviews, Revisions, and Approvals	Date

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom LHCC has no control or right of control. Providers are not agents or employees of LHCC.