

Clinical Policy: Etanercept (Enbrel)

Reference Number: CP.PHAR.250

Effective Date: 08.16

Last Review Date: 05.20

Line of Business: Medicaid

[Coding Implications](#)

[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 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

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 health plans affiliated with Centene Corporation[®] that Enbrel is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. 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 \geq 18 years;
4. Member meets one of the following (a or b):
 - a. Failure of a \geq 3 consecutive month trial of methotrexate (MTX) at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
 - b. If intolerance or contraindication to MTX (*see Appendix D*), failure of a \geq 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 baseline clinical disease activity index (CDAI) score (*see Appendix G*);
6. Dose does not exceed 50 mg every week.

Approval duration: 6 months

B. Polyarticular Juvenile Idiopathic Arthritis (must meet all):

1. Diagnosis of PJIA;
2. Prescribed by or in consultation with a rheumatologist;
3. Age ≥ 2 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, unless contraindicated or clinically significant adverse effects are experienced;
 - b. If intolerance or contraindication to MTX (*see Appendix D*), failure of a ≥ 3 consecutive month trial of sulfasalazine or leflunomide at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
5. 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

C. 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

D. 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

E. Plaque Psoriasis (must meet all):

1. Diagnosis of PsO;

2. Prescribed by or in consultation with a dermatologist or rheumatologist;
3. Age \geq 4 years;
4. Member meets one of the following (a or b):
 - a. Failure of a \geq 3 consecutive month trial of MTX at up to maximally indicated doses unless contraindicated or clinically significant adverse effects are experienced;
 - b. If intolerance or contraindication to MTX (*see Appendix D*), failure of a \geq 3 consecutive month trial of cyclosporine or acitretin at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced;
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 \geq 63 kg: 50 mg every week.

Approval duration: 6 months

F. Other diagnoses/indications

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
2. Member meets one of the following (a or b):
 - a. For RA member is responding positively to therapy as evidenced by a decrease in CDAI score since baseline (*see Appendix G*);
 - b. 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 Centene 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 for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): HIM.PHAR.21 for health insurance marketplace and CP.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 policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AS: ankylosing spondylitis
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
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 not be a formulary agent for all relevant lines of business and 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* <u>Initial dose:</u> 125 or 250 mg PO QD <u>Maintenance dose:</u> 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* <u>Initial dose:</u> 400 – 600 mg/day PO QD <u>Maintenance dose:</u> 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	20 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	RA 100 mg PO QD for 3 days, then 20 mg PO QD	
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, ibuprofen, naproxen, celecoxib)	AS Varies	Varies
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

- Contraindications:
 - Enbrel should not be administered to patients with sepsis.
- 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, pyoderma 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.
 - PsA: According to the 2018 American College of Rheumatology and National Psoriasis Foundation guidelines, TNF inhibitors or oral small molecules (e.g., methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast) are preferred over other biologics (e.g., interleukin-17 inhibitors or interleukin-12/23 inhibitors) for treatment-naïve disease. TNF inhibitors are also generally recommended over oral small molecules as first-line therapy unless disease is not severe, member prefers oral agents, or TNF inhibitor therapy is contraindicated.

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 normal 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

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
RA	25 mg SC twice weekly or 50 mg SC once weekly	50 mg/week
PsA		
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	<i>Adults:</i> <u>Initial dose:</u> 50 mg SC twice weekly for 3 months <u>Maintenance dose:</u> 50 mg SC once weekly <i>Pediatrics:</i> 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
- Multi-dose vial: 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: May 2018. Available at http://pi.amgen.com/~media/amgen/repositorysites/pi-amgen.com/enbrel/enbrel_pi.ashx. Accessed February 26, 2020.
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14. 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
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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	P&T Approval Date
Policy split from CP.PHAR.85.Psoriasis Treatments and CP.PHAR.86.Arthritis Treatments. RA, PJA, PsA, AS, PsO: Removed criteria related to HBV, malignant disease, concomitant use with other biologics, and concurrent administration of live vaccines; added dosing requirement. PJA: removed question related to number of affected joints; modified criteria to require trial of MTX, unless contraindicated; added sulfasalazine as an alternative to MTX if MTX is contraindicated. RA: changed age requirement to 18; modified criteria to require trial of MTX, unless contraindicated; added sulfasalazine and hydroxychloroquine as an alternative to MTX if MTX is contraindicated. PsO: removed duration of trial for topical and phototherapy. PsA: required trial of MTX and added requirement for the following if MTX cannot be used: leflunomide, cyclosporine, sulfasalazine & azathioprine. Re-auth: combined into All Indications; added dosing and reasons to discontinue; for PsO, changed efficacy criteria related to Psoriasis Area and Severity Index (PASI)-75 to general efficacy statement. Removed Otezla from list of therapies to trial per PDL. Modified approval duration to 6 months for initial and 12 months for renewal.	06.16	08.16
Changed age for plaque psoriasis to ≥ 4 to reflect changes in PI indication.	12.16	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. RA: Revised criteria for confirmation of diagnosis per 2010 ACR Criteria. PsO: Trial requirement modified to require the concomitant use of oral and topical or phototherapy. Safety criteria was applied according to the safety guidance discussed at CPAC and endorsed by Centene Medical Affairs.	08.17	08.17
Converted to new template. Added new dosage form Enbrel Mini. Updated appendices and references.	12.08.17	
2Q 2018 annual review: policies combined for HIM and Medicaid lines of business; modified trial and failure for RA to at least one conventional DMARD; removed TB testing for all indications; modified max dose requirements to specify pediatric and adult-specific dosing for PJIA and PsO; removed specific diagnosis requirements for PsO; removed trial and failure of phototherapy and topical therapy for PsO; added off-label criteria for HS; references reviewed and updated.	02.27.18	05.18
4Q 2018 annual review: allowed bypassing conventional DMARDs for axial PsA and required trial of NSAIDs; updated dosing for off-label indications HS; references reviewed and updated.	09.04.18	11.18
2Q 2019 annual review: removed trial and failure requirement of conventional DMARDs (e.g., MTX)/NSAIDs for biologic DMARDs for PsA per ACR/NPF 2018 guidelines; references reviewed and updated.	03.05.19	05.19
Criteria for hidradenitis suppurativa removed per 2019 North American guidelines for HS.	05.07.19	08.19
Removed HIM line of business.	12.18.19	
2Q 2020 annual review: for RA, added specific diagnostic criteria for definite RA, baseline CDAI score requirement, and decrease in CDAI score as positive response to therapy; added dose rounding guidelines for IV weight-based dosing for PJIA and pediatric PsO; references reviewed and updated.	04.23.20	05.20

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. The Health Plan 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. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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 Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. 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. The Health Plan 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 the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:

For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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