



Drug Coverage Policy

Effective Date8/15/2024
Coverage Policy Number..... IP0493
Policy Title.....Thalomid
(for Non-Oncology Uses)

Oncology – Thalomid (for Non-Oncology Uses)

- Thalomid® (thalidomide capsules – Celgene)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Cigna Healthcare Coverage Policy

Thalomid, an immunomodulatory agent, is indicated for the following uses:¹

- **Erythema nodosum leprosum (ENL)**, acute treatment of cutaneous manifestations in moderate to severe disease. Thalomid is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.
- **ENL**, maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.
- **Multiple myeloma**, newly diagnosed, in combination with dexamethasone.

Other Uses with Supportive Evidence

Discoid Lupus Erythematosus or Cutaneous Lupus Erythematosus

Thalomid has been used for discoid lupus erythematosus and cutaneous lupus erythematosus. Patients usually had refractory disease after trial of other therapies and good responses were achieved for many patients given Thalomid.²⁻¹² A retrospective medical review was done that involved 29 patients with refractory cutaneous manifestations of cutaneous lupus erythematosus who received Thalomid. Of the 23 patients who took Thalomid for 1 month, 74% of patients (n = 17/23) had complete resolution of the cutaneous manifestations and 13% of patients (n = 3/23) had a 75% or greater partial improvement.³ Another report involving patients with discoid lupus (n = 18), subacute cutaneous lupus (n = 6), and systemic lupus erythematosus with skin involvement (n = 24) who had been resistant to at least two other treatments found a response rate of 81% (n = 39/48) with use of Thalomid with 60% of patients (n = 29/48) achieving a complete cutaneous remission.⁴ Other therapies used for these conditions include antimalarial agents (e.g. hydroxychloroquine), corticosteroids (oral, topical, intralesional), methotrexate, azathioprine, cyclosporine, dapsone, mycophenolate mofetil, topical calcineurin inhibitors (e.g., Elidel[®] [pimecrolimus 1% cream], Protopic[®] [tacrolimus 0.03% and 0.1% ointment]), and Soriatane[®] (acitretin capsules).^{2,7,12}

Prurigo Nodularis

Thalomid has been studied in patients with prurigo nodularis, most of whom were refractory to other treatments or with adverse events from the other therapies.^{2,13-15} A retrospective review assessed the medical records of 42 patients with prurigo nodularis who were refractory to other therapy and who received Thalomid.¹³ Patients received Thalomid for an average of 105 weeks. Previous therapies tried included topical steroids, intralesional steroids, systemic steroids, topical tar, macrolides, cyclosporine, azathioprine, methotrexate, calcineurin inhibitors, antihistamines, dapsone, capsaicin, laser therapy, psoralen plus ultraviolet A therapy, ultraviolet B therapy, retinoids, hydroxyzine, and macrolides. With Thalomid, improvement was noted in approximately one-third of patients.

Aphthous Ulcers or Aphthous Stomatitis

Recurrent aphthous ulcers and recurrent aphthous stomatitis are associated with frequent and recurring symptoms that are painful and can lead to difficulty in speaking, eating, and swallowing.¹⁶⁻²⁷ Ulcers are larger and may persist for weeks to months. The conditions are noted in certain disease states such as in patients who are human immunodeficiency virus (HIV)-positive and Behcet's disease. In general, few adequately powered trials have assessed the efficacy of therapeutic agents for aphthous ulcers or aphthous stomatitis. Although the data are older and limited, Thalomid has led to rapid resolution of symptoms in patients with recurrent aphthous ulcers or aphthous stomatitis.¹⁶⁻²⁷ A double-blind, randomized, placebo-controlled study assessed Thalomid as a therapy for oral aphthous ulcers in patients infected with HIV. In total, 55% of patients (n = 16/29) given Thalomid had complete healing of their aphthous ulcers after 4 weeks compared with only 7% of patients (n = 2/28) who received placebo. Patients given Thalomid had symptom improvements in regards to discomfort that occurred while eating.²¹ A retrospective cohort study involving patients with recurrent aphthous stomatitis found that Thalomid was rapidly effective as 85% of patients (n = 78/92) achieved a complete remission of the condition within 14 days.²⁵ Many other agents have been used for recurrent aphthous ulcers or stomatitis including topical or intralesional corticosteroids, systemic corticosteroids, topical anesthetics/analgesics (lidocaine 2% viscous solution, benzocaine lozenges), antimicrobial mouth washes (tetracycline, chlorhexidine), topical sucralfate, acyclovir, pentoxifylline, dapsone, colchicine, and azathioprine.¹⁶⁻²⁷ Due to toxicities, use of Thalomid is generally reserved for patients who have not obtained satisfactory results with other agents.^{26,27}

Guidelines

Thalomid is addressed in guidelines from National Comprehensive Cancer Network (NCCN):

- **Castleman’s Disease:** NCCN guidelines (version 1.2024 – January 18, 2024) recommend use of Thalomid, with or without rituximab, for patients with Castleman’s disease for those who have relapsed/refractory or progressive disease (category 2A).²⁸ Thalomid is cited as an “other recommended therapy” (when given with cyclophosphamide and prednisone) for patients with multi-centric Castleman’s disease who are negative for HIV and human herpesvirus-8 (HHV-8) [category 2A].
- **Histiocytic Neoplasms:** NCCN guidelines (version 1.2024 – March 15, 2024) recommend Thalomid in a few clinical scenarios.²⁹ For Langerhans cell histiocytosis, Thalomid is recommended as first-line or as subsequent therapy for single system multifocal skin disease (including mucosa) and for relapsed/refractory disease (category 2A). Thalomid is also recommended as first-line or subsequent therapy for cutaneous skin disease associated with Rosai-Dorfman disease under “useful in certain circumstances”, irrespective of mutation (category 2A) [e.g., those with relapsed/refractory disease, symptomatic multifocal disease, symptomatic unresectable unifocal disease].
- **Kaposi Sarcoma:** NCCN guidelines (version 1.2024 – November 7, 2023) recommended Thalomid as an agent “useful under certain circumstances” for subsequent systemic therapy options for relapsed/refractory therapy (category 2A) [for patients with corticosteroid-refractory immune reconstitution inflammatory syndrome].³⁰ This includes use when given alone (in patients without HIV) or with antiretroviral therapy for patients with HIV. First-line systemic therapy options include liposomal doxorubicin (preferred), and paclitaxel. Other subsequent systemic therapy options for relapsed/refractory therapy are also cited (e.g., Pomalyst® [pomalidomide capsules] {preferred}, lenalidomide, imatinib).
- **Multiple Myeloma:** NCCN guidelines (version 4.2024 – April 26, 2024) recommend use of Thalomid in various scenarios (category 2A).³¹ It is considered “useful in certain circumstances” among patients with previously treated multiple myeloma, as well as for primary therapy for transplant candidates. Thalomid is always recommended to be used with at least two other therapies to comprise the regimen.
- **Myelofibrosis:** NCCN has guidelines regarding myeloproliferative neoplasms (version 1.2024 – December 21, 2023) that discuss myelofibrosis.³² Thalomid is recommended in the management of anemia associated with myelofibrosis “useful in certain circumstances”, with or without prednisone, for a variety of clinical scenarios (category 2A) including patients with erythropoietin levels ≥ 500 mU/mL and with erythropoietin levels < 500 mU/mL and no response or loss of response to erythropoietin stimulating agents.

The use of thalidomide (Thalomid) for oncology indications is addressed in a separate coverage policy (Oncology Medications).

Medical Necessity Criteria

Thalomid is considered medically necessary when ONE of the following is met (1, 2, 3 or 4):

FDA-Approved Indications

1. Erythema Nodosum Leprosum. Approve for 1 year.

Other Uses with Supportive Evidence

2. Discoid Lupus Erythematosus or Cutaneous Lupus Erythematosus. Approve for 1 year if the patient has tried at least two other medications.

Note: Examples of medications include corticosteroids (oral, topical, intralesional), antimalarial agents (e.g., hydroxychloroquine), topical calcineurin inhibitors (e.g., Protopic [tacrolimus

ointment], Elidel [pimecrolimus cream]), azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, dapsone, and Soriatane (acitretin capsules).

3. Prurigo Nodularis. Approve for 1 year if the patient has tried at least two other medications.

Note: Examples of medications include topical steroids, intralesional steroids, systemic steroids, topical tar, cyclosporine, macrolides, azathioprine, methotrexate, topical calcineurin inhibitors (Elidel [pimecrolimus cream], Protopic [tacrolimus ointment]), retinoids, antihistamines, hydroxyzine, dapsone, capsaicin, psoralen plus ultraviolet A therapy, and ultraviolet B therapy.

4. Recurrent Aphthous Ulcers or Aphthous Stomatitis. Approve for 1 year if the patient has tried at least two other medications.

Note: Examples of medications include topical or intralesional corticosteroids, systemic corticosteroids, topical anesthetics/analgesics (e.g., lidocaine 2% viscous solution, benzocaine lozenges), antimicrobial mouthwashes (e.g., tetracycline, chlorhexidine), topical sucralfate, acyclovir, pentoxifylline, dapsone, colchicine, and azathioprine.

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. Cancer Cachexia. Several small studies are available that have investigated Thalomid in the management of cancer cachexia related to various cancers.³³⁻³⁷ A single center double-blind, controlled trial randomized patients with pancreatic cancer who had lost at least 10% of their body weight to receive Thalomid or placebo for 24 weeks (n = 50).³⁴ Of the 33 patients evaluable at 4 weeks, patients given Thalomid had gained an average of 0.37 kg compared with a loss of 2.21 kg in the patients given placebo.³⁴ A published review of data regarding use of Thalomid for the management of cancer cachexia concluded that there is inadequate evidence to recommend Thalomid in clinical practice.³⁷

2. Crohn's Disease. Several publications report use of Thalomid in patients with Crohn's disease.³⁸⁻⁵⁴ Thalomid was used as an adjunctive therapy, or in those refractory to other therapy, and usually involved children. The data were not of high quality and primarily consisted of open-label designs or retrospective reviews, without a placebo control, and involved very few patients.³⁸⁻⁵⁴ Guidelines from the American College of Gastroenterology (2018) for the management of Crohn's disease in adults do not mention Thalomid as a therapeutic alternative.⁴⁹ Also, guidelines from the American Gastroenterological Association (2021) do not mention Thalomid in the guidelines for the medical management of moderate to severe luminal and perianal fistulizing Crohn's Disease.⁵⁵ Although some improvements were noted in published data with Thalomid, more definite data from randomized, controlled trials are required before this is a recommended therapy.⁴⁹ Consensus guidelines of the European Crohn's and Colitis Organization and the European society of Pediatric Gastroenterology, Hepatology and Nutrition (2014) state that even though some data are available that suggest efficacy of Thalomid in refractory pediatric Crohn's disease, there are insufficient data to recommend Thalomid therapy at this juncture.⁵⁴ Many other therapies are available for the management of Crohn's disease.

References

1. Thalomid® capsules [prescribing information]. Summit, NJ: Celgene Corporation; March 2023.
2. Doherty CD, Hsu S. A case series of 48 patients treated with thalidomide. *J Drugs Dermatol*. 2008;7(8):769-773.
3. Jessop S, Whitelaw DA, Grainge MJ, Jayasekera P. Drugs for discoid lupus erythematosus. *Cochrane Database Syst Rev*. 2017 May 5;(5):CD0028954.
4. Panjwani S. Early diagnosis and treatment of discoid lupus erythematosus. *J Am Board Fam Med*. 2009;22:206-213.
5. Housman TS, Jorizzo JL, McCarty MA, et al. Low-dose thalidomide therapy for refractory cutaneous lesions of lupus erythematosus. *Arch Dermatol*. 2003;139:50-54.
6. Cuadrado MJ, Karim Y, Sanna G, et al. Thalidomide for the treatment of resistant cutaneous lupus: efficacy and safety of different therapeutic regimens. *Am J Med*. 2005;118:246-250.
7. Cortes-Hernandez J, Torres-Salido M, Castro-Marrero J, et al. Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. *Br J Dermatol*. 2012;166:616-623.
8. Coehlo A, Souto MDI, Cardoso CRL, et al. Long-term thalidomide use in refractory cutaneous lesions of lupus erythematosus: a 65 series of Brazilian patients. *Lupus*. 2005;14:434-439.
9. Kuhn A, Ochsendorf F, Bonsmann. Treatment of cutaneous lupus erythematosus. *Lupus*. 2010;19:1125-1136.
10. Walling HW, Sontheimer RD. Cutaneous lupus erythematosus. Issues in diagnosis and treatment. *Am J Clin Dermatol*. 2009;10(6):365-381.
11. Hejazi EZ, Werth VP. Cutaneous lupus erythematosus: an update on pathogenesis, diagnosis and treatment. *Am J Clin Dermatol*. 2016;17(2):135-146.
12. Fairley JL, Oon S, Saracino AM, Nikpour M. Management of cutaneous manifestation of lupus erythematosus: a systematic review. *Semin Arthritis Rheum*. 2020;50(1):95-127.
13. Andersen TP, Fogh K. Thalidomide in 42 patients with prurigo nodularis Hyde. *Dermatology*. 2011;223(2):107-112.
14. Taefehnorooz H, Truchetet F, Barbaud A, et al. Efficacy of thalidomide in the treatment of prurigo nodularis. *Acta Derm Venereol*. 2011;91(3):344-345.
15. Kowalski EH, Kneiber D, Valdebran M, et al. Treatment-resistant prurigo nodularis: challenges and solutions. *Clin Cosmet Investig Dermatol*. 2019;12:163-172.
16. Chattopadhyay A, Shetty KV. Recurrent aphthous stomatitis. *Otolaryngol Clin N Am*. 2011;44:79-88.
17. Barrons RW. Treatment strategies for recurrent oral aphthous ulcers. *Am J Health-Syst Pharm*. 2010;58:41-53.
18. Messadi DV, Younai F. Aphthous ulcers. *Dermatologic Therapy*. 2010;23:281-290.
19. Chavan M, Jain H, Diwan N, et al. Recurrent aphthous stomatitis: a review. *J Oral Pathol Med*. 2012;577-583.
20. Revuz J, Guillaume JC, Janier M, et al. Crossover study of thalidomide vs. placebo in severe recurrent aphthous stomatitis. *Arch Dermatol*. 1990;126(7):923-927.
21. Jacobson JM, Greenspan JS, Spritzler J, et al, for the National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency infection. *N Engl J Med*. 1997;336:1487-1493.
22. Harte MC, Saunbury TA, Hodgson TA. Thalidomide use in the management of oromucosal disease: a 10-year review of safety and efficacy in 12 patients. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2020;130(4):398-401.
23. Belenguer-Guallar I, Jimenez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. *J Clin Exp Dent*. 2014;6(2):e168-e174.

24. Letsinger JA, McCarty MA, Jorizzo JL. Complex aphthosis: a large case series with evaluation algorithm and therapeutic ladder from topicals to thalidomide. *J Am Acad Dermatol*. 2005;52:500-508.
25. Hello M, Barbarot S, Bustuji-Garin S, et al. Use of thalidomide for severe recurrent aphthous stomatitis: a multicenter cohort analysis. *Medicine (Baltimore)*. 2010;89(3):176-182.
26. Brocklehurst P, Tickle M, Glanny AM, et al. Systemic interventions for current aphthous stomatitis (mouth ulcers). *Cochrane Database Syst Rev*. 2012 Sep 12;9:CD005411.
27. Shetty K. Current role of thalidomide in HIV-positive patients with recurrent aphthous ulcerations. *Gen Dent*. 2007;55(6):537-542.
28. The NCCN Castleman's Disease Clinical Practice Guidelines in Oncology (version 1.2024 – January 18, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on May 28, 2024.
29. The NCCN Histiocytic Neoplasms (version 1.2024 – March 15, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on May 28, 2024.
30. The NCCN Kaposi Sarcoma Clinical Practice Guidelines in Oncology (version 1.2024 – November 7, 2023). © 2023 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on May 28, 2024.
31. The NCCN Multiple Myeloma Clinical Practice Guidelines in Oncology (version 4.2024 – April 26, 2024). © 2024 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on May 28, 2024.
32. The NCCN Myeloproliferative Neoplasms Clinical Practice Guidelines in Oncology (Version 1.2024 – December 21, 2023). © 2023 National Comprehensive Cancer Network. Available at: <http://www.nccn.org>. Accessed on May 28, 2024.
33. Mantovani G, Maccio A, Madeddu C, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. *Oncologist*. 2010;15:200-211.
34. Gordon JN, Trebble TM, Ellis RD, et al. Thalidomide in the treatment of cancer cachexia: a randomized placebo-controlled trial. *Gut*. 2005;54:540-545.
35. Khan ZH, Simpson EJ, Cole AT, et al. Oesophageal cancer and cachexia: the effect of short-term treatment with thalidomide on weight loss and mean body mass. *Aliment Pharmacol Ther*. 2003;17:677-682.
36. Davis M, Lasheen W, Walsh D, et al. A phase II dose titration study of thalidomide for cancer-associated anorexia. *J Pain Symptom Manage*. 2012;43(1):78-86.
37. Reid J, Mills M, Cantwell M, Cardwell CR, et al. Thalidomide for managing cancer cachexia (Review). *Cochrane Database Syst Rev*. 2012 Apr 18;4:CD008664.
38. Sabate JM, Willarejo J, Lemann M, et al. An open-label study of thalidomide for maintenance therapy in responders to infliximab in chronically active and fistulizing refractory Crohn's disease. *Aliment Pharmacol Ther*. 2002;16:1117-1124.
39. Plamondon S, Ng SC, Kamm MA. Thalidomide in luminal and fistulizing Crohn's disease resistant to standard therapies. *Aliment Pharmacol Ther*. 2007;25:557-567.
40. Lazzerini M, Martelossi S, Marchetti F, et al. Efficacy and safety of thalidomide in children and young adults with intractable inflammatory bowel disease: long-term results. *Aliment Pharmacol Ther*. 2007;25:419-427.
41. Lazzerini M, Martelossi S, Magazzu G, et al. Effect of thalidomide on clinical remission in children and adolescents with refractory Crohn's disease. A randomized clinical trial. *JAMA*. 2013;310(20):2164-2173.
42. Felipez LM, Gokhale R, Tierney MP, Kirschner BS. Thalidomide use and outcomes in pediatric patients with Crohn disease refractory to infliximab and adalimumab. *JPGN*. 2012;54:28-33.
43. Gerich ME, Yoon JL, Targan SR, et al. Long-term outcomes of thalidomide in refractory Crohn's disease. *Aliment Pharmacol Ther*. 2015;41(5):429-437.
44. Akobeng AK, Strokkers PC. Thalidomide and thalidomide analogues for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2009 Apr 15(2):CD007351.
45. Srinivasan R, Akobeng AK. Thalidomide and thalidomide analogues for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2009 Apr 15(2):CD007350.

46. Facchini S, Candusso M, Martellosi S, et al. Efficacy of long-term treatment with thalidomide in children and young adults with Crohn’s disease: preliminary results. *J Pediatric Gastroenterol Nutr.* 2001;32(2):178-181.
47. Vasiliauskas AE, Kam LY, Abreu-Martin MT, et al. An open-label pilot study of low-dose thalidomide in chronically active, steroid-dependent Crohn’s disease. *Gastroenterol.* 1999;117(6):1278-1287.
48. Ehrenpreis ED, Kane SV, Cohen LB, et al. Thalidomide therapy for patients with refractory Crohn’s disease: an open-label trial. *Gastroenterol.* 1999;117(6):1271-1277.
49. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG clinical guideline: Management of Crohn’s disease in adults. *Am J Gastroenterol.* 2018;113(4):481-517.
50. Simon M, Pariente B, Lambert J, et al. Long-term outcomes of thalidomide therapy for adults with refractory Crohn’s disease. *Clin Gastroenterol Hepatol.* 2016;14(7):966-972.
51. Yang C, Singh P, Singh H, et al. Systematic review: thalidomide and thalidomide analogues for treatment of inflammatory bowel disease. *Aliment Pharmacol Ther.* 2015;41:1079-1093.
52. Bramuzzo M, Ventura A, Martellosi S, Lazzerini M. Thalidomide for inflammatory bowel disease. Systematic review. *Medicine (Baltimore).* 2016;95(30):e4239.
53. Kammermeier J, Morris MA, Garrick V, et al, for the BSPGHAN IBD Working Group. Management of Crohn’s disease. *Arch Dis Child.* 2016;101:475-480.
54. Ruemmele FM, Veres G, Volho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn’s disease. *J Crohns Colitis.* 2014;8(10):1179-1207.
55. Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's Disease. *Gastroenterology.* 2021;160(7):2496-2508.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	<p>All uses with 'tried' criteria.</p> <p>Updated formatting to examples of alternatives.</p> <p>Updated title from Thalomid Non-Oncology Uses</p>	8/15/2024

The policy effective date is in force until updated or retired.

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