EXPRESS SCRIPTS®

PRIOR AUTHORIZATION POLICY

POLICY: Oncology – Thalomid® (thalidomide capsules – Celgene)

TAC APPROVAL DATE: 03/20/2019

OVERVIEW

Thalomid is indicated for use in combination with dexamethasone for the treatment of patients with newly diagnosed multiple myeloma.[1] It is also indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). It is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis. Thalomid is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

Guidelines

The National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma (version 2.2019 – November 16, 2018) recommend use of Thalomid in various scenarios.[2] It is considered useful in certain circumstances among patients with previously treated multiple myeloma, as well as for primary therapy for transplant candidates.

The National Comprehensive Cancer Network (NCCN) has guidelines regarding myeloproliferative neoplasms (version 2.2019 – October 29, 2018) that discuss myelofibrosis.[3] Thalomid is recommended in the management of anemia associated with myelofibrosis, with or without prednisone, for patients with erythropoietin levels ≥ 500 mU/mL.

NCCN guidelines for systemic light chain amyloidosis (version 1.2019 – October 26, 2018) cite Thalomid in combination with dexamethasone, with or without cyclophosphamide, as a therapeutic consideration, along with best supportive care, for patients with organ involvement based on amyloidosis consensus criteria (category 2A recommendation).[4]

The NCCN guidelines for acquired immune deficiency syndrome (AIDS)-Related Kaposi Sarcoma (version 2.2019 – November 29, 2018) recommended Thalomid for subsequent systemic therapy options for relapsed/refractory therapy.[5] 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], imatinib).

The National Comprehensive Cancer Network (NCCN) guidelines for B-Cell Lymphomas (version 2.2019 – November 16, 2018) recommend use of Thalomid, with or without Rituxan, for patients with Castleman's disease who have relapsed/refractory or progressive disease.[6]

Other Uses with Supportive Evidence

Some data support the use of Thalomid for ENL, although the condition is not common and data are limited.[7,8] Data indicates that Thalomid does successfully and quickly improve the cutaneous manifestations of ENL and in some patients the steroid requirement was reduced.

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.[9-18] A retrospective medical review was done and 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.[12] 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.[13] 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, Protopic) and Soriatane.[11,16]

Thalomid has been studied in myelofibrosis.[19-23] In a Phase II investigation (n = 21), low-dose Thalomid, given with prednisone, led to 40% of patients (n = 4/10) who were dependent upon transfusions to become transfusion-independent.[23] In another Phase II trial involving patients who had myelofibrosis with myeloid metaplasia (n = 41), 41% of patients who received Thalomid for at least 15 days achieved a response.[20] Jakafi® (ruxolitinib tablets) is indicated for the treatment of patients with myelofibrosis.[24] Other treatment options in myelofibrosis include androgens, Epogen, Procrit, Aranesp, prednisone, danazol, Revlimid, melphalan, Myleran, alfa interferons, and hydroxyurea.[25-26]

Thalomid has been studied in patients with prurigo nodularis, most of whom were refractory to other treatments or with adverse events (AEs) from the other therapies.[9,27,28] A retrospective review assessed the medical records of 42 patients with prurigo nodularis who were refractory to other therapy and who received Thalomid.[27] 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, calcineurnin inhibitors, antihistamines, dapsone, capsaicin, laser therapy, PUVA, UVB, retinoids, hydroxyzine, and macrolides. With Thalomid, improvement was noted in approximately one-third of patients.

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.[29-32] 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 Bechet's disease. In general, few adequately powered trials have assessed the efficacy of therapeutic agents for aphthous ulcers or aphthous stomatitis.[29] Although the data are older and limited, Thalomid has led to rapid resolution of symptoms in patients with recurrent aphthous ulcers or aphthous stomatitis.[33-38] 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.[34] 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.[38] 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 sulcralfate, acyclovir, pentoxifylline,

dapsone, colchicine, and azathioprine.[29-32] Due to toxicities, use of Thalomid is generally reserved for patients who have not obtained satisfactory results with other agents.[39,40]

Data are also available regarding use of Thalomid for systemic light chain amyloidosis.[41,42] Thalomid has combined with cyclophosphamide and dexamethasone which led to a complete hemalogical response in 74% of patients (n = 48/65).[42] Thalomid has also been used for patients Waldenstrom's macroglöbulinemia.[43-44] with A Phase II study used Thalomid with Rituxan in patients with symptomatic Waldenström's macroglobulinemia (n = 25).[44] The regimen was associated with an approximate overall response rate of 70%, and a median progression-free survival of 3 years.[44-

Safety

Thalomid has a Boxed Warning regarding embryofetal toxicity and venous thromboembolism. The safety and effectiveness in pediatric patients < 12 years of age have not been established. Thalomid is available only through the THALOMID Risk Evaluation Mitigation Strategy (REMS™) program. Males and females must follow the required reproductive precautions.

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Thalomid. All approvals are provided for 3 years in duration.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Thalomid is recommended in those who meet the following criteria:

FDA-Approved Indications

1. **Erythema Nodosum Leprosum (ENL).** Approve for 3 years.

2. **Multiple Myeloma.** Approve for 3 years.

Other Uses with Supportive Evidence

3. **Acquired Immune Deficiency Syndrome (AIDS)-Related Kaposi's Sarcoma.** Approve for 3 years if the patient meets the following (A and B):
   - **A)** The patient has tried one regimen or therapy (e.g., liposomal doxorubicin, paclitaxel, Pomalyst® [pomalidomide capsules], imatinib); AND
   - **B)** The patient has relapsed or refractory disease.

4. **Castleman's Disease.** Approve for 3 years in patients with relapsed/refractory or progressive disease.

5. **Discoid Lupus Erythematosus or Cutaneous Lupus Erythematosus.** Approve for 3 years if the patient has tried two other therapies (e.g., 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]).

6. **Myelofibrosis.** Approve for 3 years if the patient has tried one other therapy (e.g., Jakafi® [ruxolitinib tablets] androgens [e.g., nandrolone, oxymetholone], danazol, Epogen®/Procrit® [epoetin alfa injection], Aranesp® [darbepoetin alfa injection], prednisone, Revlimid® [lenalidomide capsules], melphalan, Myleran® [busulfan tablets], alfa interferons, and hydroxyurea).

7. **Prurigo Nodularis.** Approve for 3 years if the patient has tried two other therapies (e.g., topical steroids, intralesional steroids, systemic steroids, topical tar, cyclosporine, macrolides, azathioprine, methotrexate, topical calcineurin inhibitors [Elidel, Protopic], retinoinds, antihistamines, hydroxyzine, dapsone, capsaicin, psoralen plus ultraviolet A [PUVA] therapy, ultraviolet B [UVB] therapy).

8. **Recurrent Aphthous Ulcers or Aphthous Stomatitis.** Approve for 3 years if the patient has tried two other therapies (e.g., topical or intralesional corticosteroids, systemic corticosteroids, topical anesthetics/analgesics [e.g., lidocaine 2% viscous solution, benzocaine lozenges], antimicrobial mouthwashes [e.g., tetracycline, chlorhexidine], topical sulcralfate, acyclovir, pentoxifylline, dapsone, colchicine, and azathioprine).

9. **Systemic Light Chain Amyloidosis.** Approve for 3 years.

10. **Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma.** Approve for 3 years.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Thalomid has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Breast Cancer.** Two Phase II studies assessed the use of Thalomid in metastatic breast cancer.[45,46] One trial examined use of Thalomid with Xeloda® (capecitabine tablets) in 24 patients with previously treated metastatic breast cancer and the results do not support a role of Thalomid, which was also poorly tolerated.[46] A Phase II trial involved 28 patients with progressive metastatic breast cancer and no patient had a true partial or complete response with Thalomid; data do not support use of Thalomid as a single agent.[45] The NCCN guidelines for breast cancer (version 1.2019 – March 14, 2019) do not mention Thalomid as a therapeutic alternative.[47]

2. **Cancer Cachexia.** Several small studies are available that have investigated Thalomid in the management of cancer cachexia related to various cancers.[48-51] 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).[49] 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.[49] 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.[52]

3. **Crohn's Disease.** Several publications report use of Thalomid in patients with Crohn's disease.[53-69] 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.[53-63] 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.[64] 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.[64] Consensus guidelines of the European Crohn's and Colitis Organization (ECCO) and the European society of Pediatric Gastroenterology, Hepatology and Nutrition (ESOGGAN) [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 recommended Thalomid therapy at this juncture.[69] Many other therapies are available for the management of Crohn's disease.

4. **Glioblastoma Multiforme.** Only limited data have investigated the use of Thalomid in patients with glioblastoma multiforme.[70-75] A Phase II trial studied a regimen of Temodar® (temozolomide capsules) given on Days 1 through 5 of each 28-day cycle and Thalomid given once daily at bedtime in patients (n = 44) who had recurrent glioblastoma multiforme after surgery, radiotherapy and/or adjuvant chemotherapy.[73] Thalomid added to Temodar did not display improvement in therapy beyond what is anticipated with Temodar.[73] Other Phase II studies suggests Thalomid has minimal activity as a single agent or in combination with other therapies (e.g., irinotecan).[70-75] The NCCN guidelines for central nervous system cancers (version 1.2019 – March 5, 2019), which address therapies for glioblastomas, do not suggest Thalomid as a therapeutic alternative.[76]

5. **Hepatocellular Carcinoma.** Only limited data have investigated the use of Thalomid in patients with hepatocellular carcinoma.[77-79] Most trials were retrospective reviews or Phase II or I/II trials that generally showed little activity of the agent. The NCCN guidelines for hepatobiliary cancers (version 2.2019 – March 6, 2019) do not mention Thalomid as a therapeutic alternative.[80]

6. **Metastatic Renal Cell Carcinoma.** Several studies have investigated the use of Thalomid in patients with metastatic renal cell carcinoma.[81-83] A Phase II trial involving 20 patients with metastatic renal cell carcinoma assessed the efficacy of interferon combined with Thalomid and concluded that the combination has minimal efficacy and considerable toxicity.[81] NCCN guidelines for kidney cancer (version 3.2019 – February 6, 2019) do not mention Thalomid as a treatment option in metastatic renal cell carcinoma.[84] Further investigation is needed before the role of Thalomid is defined in metastatic renal cell carcinoma.

7. **Myelodysplastic Syndrome (MDS).** Only limited data have investigated the use of Thalomid in patients with MDS.[85-87] The NCCN guidelines for MDS (version 2.2019 – October 18, 2018) do not list Thalomid as a therapeutic alternative.[88] A Thalomid analogue, Revlimid® (lenalidomide capsules), is indicated for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-risk MDS associated with a deletion of 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.[89]

8. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Annual revision	No criteria changes.	03/01/2017
Annual revision	No criteria changes.	03/07/2018
Annual revision	Added approval for patients with acquired immune deficiency syndrome (AIDS)-Related Kaposi's Sarcoma for 3 years if the patient has tried one regimen therapy (e.g., liposomal doxorubicin, paclitaxel, Pomalyst® [pomalidomide capsules], imatinib) and the patient has relapsed or refractory disease. Added criteria to approve for Castleman's disease in patients with relapsed/refractory or progressive disease.	03/20/2019

TAC – Therapeutic Assessment Committee; * For a further summary of criteria changes, refer to respective TAC minutes available at: http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx.