Clinical Edit Criteria Proposal

Drug/Drug Class: **THALOMID@ (thalidomide)**

Prepared for: Missouri Medicaid
Prepared by: Heritage Information Systems, Inc.

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:
The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis, apply clinical edit or require prior authorization for use.

Dosage Forms & Manufacturer:
50, 100, & 200 mg capsules.
Celgene Corporation

Summary of Findings:
Thalomid@ (Thalidomide) is a immunomodulatory agent for treatment of erythema nodosum leprosum (ENL), a complication of leprosy, and treatment refractory Crohn's disease patients. Additionally, this drug is being used for a number of off-label, but well documented in peer-reviewed literature, uses including AIDS-related aphthous stomatitis, multiple myeloma, and GVH reaction. All prescribers and dispensing pharmacist of Thalomid must register under a special distribution program at Celgene that has been approved by the FDA.

Status Recommendation:
☐ Prior Authorization (PA) Required ☐ Open Access
☒ Clinical Edit

Type of PA Criteria:
☐ Increased Risk of ADE ☐ Non-Preferred Agent
☒ Appropriate Indications ☐ PA Not Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis, apply clinical edit or require prior authorization for use. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guiding appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction[1]

Thalidomide first entered clinical practice outside the United States in the late 1950s as a sedative and as a remedy for morning sickness during pregnancy. Many women took the drug before its severe teratogenic potential was known. Almost 10,000 children worldwide were affected with fetal malformations involving the extremities (phocomelia), ears, eyes, and gastrointestinal tract. Thalidomide was withdrawn from the market in 1962. After numerous studies began to reveal the immunomodulatory and antiangiogenic properties of the drug, it reentered clinical practice despite its tragic history. The Food and Drug Administration approved thalidomide in 1998 for treatment of erythema nodosum leprosum. It also has been prescribed to treat acquired immunodeficiency syndrome-related cachexia, aphthous ulcers, chronic graft-versus-host disease, and a variety of solid and hematologic tumors.

Dosage Form(s)[2]

Thalomid is available in 50, 100, & 200 mg capsules from Celgene Corporation

Manufacturer[2]

Celgene Corporation, Warren, NJ

Indication[1,2]

Thalomid@ (thalidomide) is labeled by the US Food and Drug Administration (FDA) for acute treatment of cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) in leprosy patients and for maintenance therapy for prevention and suppression of cutaneous manifestations of ENL recurrence. The drug has been designated an orphan drug by the US Food and Drug Administration (FDA) for the treatment of ENL and treatment and maintenance of reactional The drug has been designated an orphan drug by the US Food and Drug Administration (FDA) for the treatment of ENL and treatment and maintenance of reactional lepromatous leprosy. Thalidomide also has been designated an orphan drug by the FDA for treatment of wasting syndrome associated with human immunodeficiency virus (HIV) infection; prevention and treatment of severe recurrent aphthous stomatitis in severely, terminally immunocompromised patients; prevention and treatment of graft-versus-host disease in patients receiving bone marrow transplantation; treatment of multiple myeloma; treatment of clinical manifestations of mycobacterial infection caused by *Mycobacterium tuberculosis* and nontuberculous mycobacteria; treatment of Crohn's disease; and treatment of primary brain tumors. In addition, thalidomide has been used for the treatment of a variety of inflammatory

and/or dermatologic disorders, treatment of various HIV-associated conditions, and treatment of various malignancies.

Clinical Efficacy[5-6] (mechanism of action/pharmacology, comparative efficacy)

Thalidomide is an immunomodulatory agent with anti-inflammatory activity. The drug also has anti-angiogenic effects and sedative and hypnotic effects. The drug also has anti-angiogenic effects and sedative and hypnotic effects. The mechanism(s) of action of the immunomodulatory and anti-inflammatory effects of thalidomide are complex and have not been fully determined; these effects appear to result in part from modulation of tumor necrosis factor alpha (TNF-α) levels, costimulatory or adjuvant effect on T-cells resulting in increased T-cell proliferation and increased production of interleukin-2 and interferon-γ, and/or modulation of leukocyte migration and chemotaxis. The immunomodulatory and anti-inflammatory effects of thalidomide differ from those of other immunosuppressive agents, including corticosteroids, cyclosporin (e.g., cyclosporine) or macrolide (e.g., tacrolimus) immunosuppressants, pentoxifylline, immunosuppressive purine analogs (e.g. azathioprine) and purine metabolism inhibitors (e.g., mycophenolic acid), and also differ from those of nonsteroidal anti-inflammatory agents. Thalidomide does not appear to interfere with important host antimicrobial mechanisms; the drug has no substantial inhibitory effect on lymphocyte proliferation, does not impair delayed-type hypersensitivity reactions, and does not impair granuloma formation. Thalidomide has no direct antibacterial activity against *Mycobacterium leprae*. In addition, results of an in vitro study using *Enterocytozoon bieneusi*, *Encephalitozoon intestinalis*, and *E. cuniculi* indicate that thalidomide has no direct activity against microsporidia.

The pharmacokinetics of thalidomide have been studied in healthy adults, adults with leprosy, adults with human immunodeficiency virus (HIV) infection, and geriatric men with prostate cancer. While there is some evidence that bioavailability of oral thalidomide (i.e., peak plasma concentrations, area under the plasma concentration-time curve [AUC]) may be greater in leprosy patients than in healthy individuals, results of a single-dose study indicate that the pharmacokinetics of thalidomide in HIV-infected individuals are similar to those in healthy individuals. Age-related changes in the pharmacokinetics of thalidomide have not been observed in healthy individuals, leprosy patients 20–69 years of age, or prostate cancer patients 55–80 years of age. The pharmacokinetics of thalidomide have not been studied to date in individuals younger than 18 years of age. While limited data indicate that the pharmacokinetics of thalidomide are similar in males and females, specific comparative studies have not been performed to determine whether there are any gender- or race-related differences in the pharmacokinetics of the drug. The pharmacokinetics of thalidomide in patients with renal or hepatic impairment have not been determined. Based on studies in healthy adults and HIV-infected patients, the pharmacokinetics of thalidomide can best be described by a single-compartment model with first-order absorption and elimination. Results of studies in healthy adults indicate that accumulation of thalidomide does not occur, and pharmacokinetic parameters are similar following single or multiple doses of the drug.

Adverse Effects[4]

Thalomid[@] is contraindicated in the following conditions:

- Child-bearing female planning to get pregnant within the next 1½ year or pregnant
- Breast feeding
- Severe chronic neutropenia

Additionally, patients who have hypotension or bradycardia should be monitored.

The most serious toxicity associated with Thalomid is its documented tetratogenicity. The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy. Thalidomide is associated with drowsiness/somnolence (37.5%), peripheral neuropathy (8.3%), dizziness/orthostatic hypotension (8.3%), neutropenia (12.5%), and HIV-viral load increase (18.7%). Somnolence, dizziness, and rash are the most commonly observed adverse events.

Drug Interactions

Thalomid® has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine.

Dosage and Administration[4]

The dose for cutaneous ENL: initiate dosing at 100-300 mg/day taken once daily at bedtime with water (at least 1 hour after evening meal). Patients weighing < 110 lbs. Initiate therapy at the lower end of the losing range. Severe reaction or previously requiring high dose may be initiated at 400mg/day; doses may be divided, but taken 1 hour after meals. Dosing should continue until active reaction subsides (usually 2 weeks), then taper to 50 mg decrements every 2-4 weeks.
For off-label use dosing demonstrated in phase III clinical trials for the following indications:
Behcet's syndrome: 100-400 mg/day
Graft-vs-Host Reactions: 100-1600 mg/day; usual initial dose: 200 mg 4 times/day up to 7 days.
AIDS-related aphthous stomatitis: 200 mg twice a day for 5 days, then 200 mg/day for up to 8 weeks.
Discoid lupus erythematosus: 100-400 mg/day; maintenance dose: 25-50 mg.

Cost Comparison[6] (at commonly used dosages)

Drug	Dose	Monthly Cost (AWP)
Thalomid 50mg	100-400mg/day (Labeled use)	$492.84 –1,971.36
Thalomid 50mg	100-1600 mg/day (off-label)	$492.84- $7,910.40
Thalomid 100 mg	100-400mg/day (Labeled use)	$1,234-$4,937.15
Thalomid 100 mg	100-1600 mg/day (Labeled use)	$1,234-$19,890

Conclusion

In conclusion, Thalomid is indicated for ENL and several off-label indications, including multiple myeloma, Graft vs. Host Reaction, AIDS-related aphthous stomatitis, etc. Phase III clinical trials are underway for most of the off-label indications. Since evaluation of the off-label indications are still underway, Thalomid should be reserved as a second line therapy.

Recommendation(s)

It is recommended that a clinical edit be applied to Thalomid.

Approval Criteria

- Diagnosis of cancer or leprosy in last 2 years

Recommendation(s)

- Inappropriate diagnosis

References

1. Rajkumar SV. Current status of thalidomide in the treatment of cancer. Oncology 2001;15:867-74.
2. Short RM, Burnham TH, et.al., editors. Facts and Comparisions. Missouri: Facts and Comparisons.
3. Anon. New uses of thalidomide. *Med Lett Drugs Ther*. 1996; 38:15-6
4. Celegene. Thalomid® package labeling. January 2003.
5. Medical Economics. 2003 RedBook Update. March 2003;22(3).

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