DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 25 2006

The Honorable Richard Blumenthal
Attorney General of the State of Connecticut
55 Elm Street, P.O. Box 120
Hartford, CT 06141-0120

Re: Docket No. 2005P-0167/CP1

Dear Mr. Attorney General:

This letter responds to your citizen petition (Petition) dated May 4, 2005. In the petition, you raise concerns related to the off-label use of Thalomid (thalidomide) for the treatment of multiple myeloma and other blood-related cancers. Specifically, your concerns relate to the increased potential for serious blood clots when Thalomid is used to treat multiple myeloma and other cancers, particularly when used in combination with other cancer-treatment therapies. In conjunction with these concerns, you request that the Food and Drug Administration (FDA) require Celgene, the holder of the approved application for Thalomid, to take the following actions (Petition at 3-4):

- Strengthen Thalomid's "black box" warning statement (boxed warning) concerning the heightened risk of blood clotting;
- Supplement the labeling with additional bolded warnings;
- Conduct a phase IV clinical trial addressing the risks and benefits of prophylactic therapies to limit the risk of blood clots;
- Issue a "Dear Healthcare Professional" letter notifying prescribers of the increased potential for serious blood clots when Thalomid is used in combination with other cancer-treatment therapies; and
- Expand Thalomid's risk management program.[1]

FDA has carefully considered the information submitted in your petition and a variety of other relevant data obtained by the Agency. Based on our review of these materials, and for the reasons described below, your petition is granted in part and denied in part.

[1] You also suggest that FDA might have authority over Celgene's pricing of Thalomid, under Subpart H (Petition at 24). However, because your petition does not tie any specific request to this suggestion, the Agency declines to address it in this response.

I. BACKGROUND

Thalomid is a marketed brand of the drug thalidomide. Thalidomide was first synthesized in 1957 and was approved in Europe the following year.[2] By 1959, thalidomide was marketed in 48 countries as a mild sedative and antiemetic, available in many areas without a prescription.

In 1960, an application was submitted to FDA to market thalidomide as a sedative. This application was not approved because of emerging reports linking use of thalidomide to neuropathy.[3] While the Agency was waiting for more information about these safety concerns, the link between thalidomide use and congenital malformations in Europe was recognized. The drug was withdrawn from the market worldwide. However, an estimated 5,000 to 6,000 infants were born with characteristic thalidomide-induced deformities (phocomelia or amelia of the limbs, frequently combined with cardiovascular, gastrointestinal, respiratory, or urogenital defects).

In 1965, a serendipitous observation of improvement during thalidomide use in patients with erythema nodosum leprosum (ENL)[4] was confirmed by clinical trials,[5] and, in 1988, thalidomide was licensed in Mexico for this indication. In September 1997, FDA's Dermatologic and Ophthalmologic Drug Advisory Committee voted 6-1 that thalidomide was effective for the treatment of ENL and, later that same month, an open public scientific workshop was held to discuss the potential risks and benefits of thalidomide use. On July 16, 1998, FDA approved Thalomid (NDA 20-785) with the limited indication of treating cutaneous manifestations of moderate to severe ENL and preventing recurrence of the cutaneous manifestations of ENL. At the time of approval, FDA required a strict risk management program under our regulations in 21 CFR part 314, subpart H (see § 314.520). Celgene developed the System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.) to meet FDA's requirements.

The S.T.E.P.S. program imposes the following requirements:

- Distribution of Thalomid only by prescribers and pharmacies registered with the program;

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[2] See Kunz W., 1956; see also Thalidomide: Potential Benefits and Risks, Open Public Scientific Workshop, September 9-10, 1997, http://odp.od.nih.gov/ord/thalidom.pdf (reviewing the historical development of thalidomide). Full references for all of the clinical studies cited in this response are provided in the enclosed alphabetized reference list.

[3] See Burley D., 1961; Fullerton P.M., Kremer M., 1961.

[4] ENL is a condition that develops in some patients with Hansen's disease (leprosy), usually after they have been in treatment for a period of time. ENL typically manifests as crops of tender, erythematous papules, plaques, or nodules, accompanied by extracutaneous conditions including fever, neuritis, and arthritis.

[5] See Sheskin J., 1965.

- Completion of printed and video educational materials and acquisition of individual patient informed consent;

- Agreement by patients to comply with the provisions of the program, including agreement not to share medication or donate blood or sperm;

- Agreement by female users of childbearing potential to use two methods of birth control and undergo periodic pregnancy testing;

- Agreement by male users to use barrier contraception when sexually active with a female of childbearing potential; and

- A restriction on prescribing or dispensing more than a 28 day supply of the drug.

In the years since the initial United States approval of thalidomide, a body of literature has emerged indicating that the drug is helpful in the treatment of multiple myeloma, and there has been increased use of thalidomide to treat this condition. In fact, currently, Thalomid is prescribed most frequently for the treatment of multiple myeloma (Petition at 1). The S.T.E.P.S. program has been successful in preventing thalidomide-induced birth deformities, and Thalomid's distribution and use continue to be managed by the program.

Today, FDA is approving a supplement to NDA 20-785, adding an indication for the treatment of patients with newly diagnosed multiple myeloma. As discussed in more detail below, the labeling for Thalomid has been revised in conjunction with our approval of the supplement. The issues raised in your petition were considered by the Agency in the course of making these labeling revisions.

II. DISCUSSION

A. Strengthening of Thalomid's Labeling

You ask that FDA require Celgene to revise Thalomid's labeling in several ways, including by adding new cautionary language to Thalomid's boxed warning and adding bolded warnings cautioning healthcare providers and patients about the increased risk of venous thromoboembolism (VTE) when Thalomid is used to treat multiple myeloma and other malignant conditions and, particularly, when Thalomid is used to treat these conditions in conjunction with corticosteroid therapy and chemotherapy agents. We address each of your requests in turn.

1. Boxed Warning

You request that FDA require Celgene to strengthen Thalomid's boxed warning to heighten the warning of the risk of VTE. Specifically, you request that the boxed warning currently in place be supplemented with the following language (Petition at 11):

> In malignant conditions, such as multiple myeloma, patients are predisposed to a hypercoagulable state. Thus, caution should be used when Thalomid is combined with chemotherapy, as venous thromboembolism is a potential complication. An unexpectedly high risk of venous thromboembolism has been observed when Thalomid is combined with chemotherapy for newly diagnosed patients with myeloma. The potential for experiencing thrombotic events is particularly acute when Thalomid is used concomitant with vincrisine, doxorubicin and dexamethasone.

FDA's regulation at § 201.57(e) (21 CFR 201.57(e))[6] describes the requirements for warnings in prescription drug labeling and sets forth the circumstances in which boxed warnings are appropriate. Section 201.57(e) provides in pertinent part:

> Under this [Warnings] section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved . . . . Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.

We agree that a revision of Thalomid's boxed warning to incorporate new information about thromboembolic risk is warranted based on our review of the published medical literature regarding the risk of VTE during thalidomide treatment for multiple myeloma. We have conducted a thorough review of the medical literature concerning the risk of VTE in multiple myeloma patients treated with thalidomide and, consistent with the analysis of the Research on Adverse Drug events And Reports (RADAR) project appended to your petition, have identified 19 relevant studies.[7] Based on these 19 clinical

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[6] On June 30, 2006, the effective date of the Physician Labeling Rule, current § 201.57(e) will be recodified as § 201.80(e) (21 CFR 201.80(e)).

[7] These 19 clinical studies, all of which are identified with full citations in the attached reference list, are: Abdelkefi A., Torjman L., Ben Romdhane N., et al., 2005; Anagnostopoulos A., Weber D., Rankin K., et al., 2003; Arnulf B., Levy V., Leblond V., et al., 2003; Cavo M., Zamagni E., Tosi P., et al., 2005; Dimopoulos M.A., Zervas K., Kouvatseas G., et al., 2001; Klueppelberg U., Shapira I., Chen L., et al., 2005; Kropff M.H., Lang N., Bispin G., et al., 2003; Ludwig H., Drach J, Tóthová, E., et al., 2005; Osman K., Rajkumar S.V., 2001; Palumbo A., Bertola A., Musto P., et al., 2004; Rajkumar S.V., Gertz M.A., Lacy M.Q., et al., 2003; Rajkumar S.V., Hayman S., Gertz M.A., et al., 2002; Schutt P., Ebeling P., Buttkereit U., et al., 2005;Wang M., Weber D.M., Delasalle K., et al., 2005; Weber D., Rankin K., Gavino M., et al., 2003; Zangari M., Anaissie E., Barlogie B., et al., 2001; Zangari M., Saghafifar F., Mehta P., et al., 2003; Zangari Z., Siegel E., Barlogie B., 2002; Zervas K., Dimopoulas M.A., Hatziharissi E., et al., 2003.

studies,[8] we have calculated the reported risk of VTE as ranging from approximately 3 to 5 percent when thalidomide is used alone, reaching up to 8 percent when thalidomide is combined with dexamethasone, and ranging from 8 to 28 percent when thalidomide is used in combination with standard chemotherapeutic agents such as alkylating agents or anthracyclines. These data suggest that the risk of VTE in multiple myeloma patients nearly doubles during treatment with combination regimens containing both thalidomide and other chemotherapeutic agents, as compared to treatment in which thalidomide is used alone.

Based on the information discussed above, and in keeping with the clinical evidence currently available, we have requested and Celgene has agreed to insert the following language into its boxed warning:

> The use of Thalomid® (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

This language gives healthcare providers an overview of the known risk of VTE associated with thalidomide use and of the existence of potential prophylaxis. We believe that this language better describes the risk of thromboembolic events in connection with Thalomid use than the boxed warning language that you propose, because it specifically identifies the available data and the availability of potential prophylactic measures.

While you have not requested that the boxed warning contain information about the use of prophylactic anticoagulation therapies, we believe that it should. There is evidence that prophylactic anticoagulation therapies prescribed in conjunction with thalidomide may lessen the potential for VTE events. In four recent studies evaluating thalidomide

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[8] Unlike the RADAR project report, which relies upon data pertaining to VTE in patients with a variety of cancers who have been treated with thalidomide, we have specifically focused our analysis on reports concerning the risk of VTE in multiple myeloma patients who have been treated with thalidomide.

plus dexamethasone for newly diagnosed multiple myeloma, the authors observed clusters of VTE among those patients who began participating in these studies earliest. These four study protocols were, therefore, amended to include prophylactic antithrombotic therapy with heparin, full-dose warfarin, or aspirin, and subsequent rates of VTE appeared lower.[9] The preliminary uncontrolled data reported in the four studies suggest that when prophylactic antithrombotic therapy is used in conjunction with thalidomide treatment, the potential for VTE may be reduced.

Despite the promise of these antithrombotic therapies, they are not without their own serious risk to patients, particularly to cancer patients; therefore, the warning language that we have approved is not as forceful as the language concerning prophylaxis that you propose for inclusion in other portions of the labeling (Petition at 11-12). Anticoagulation for prophylaxis has been associated with severe and fatal bleeding (as outlined in the warfarin labeling), and cancer patients can have an already increased risk of bleeding and clotting based on their underlying disease.[10] This risk is compounded for multiple myeloma patients who are at risk of falls and pathologic fractures, which can be complicated by bleeding.[11] Therefore, prophylactic measures are not appropriate in all cases, and any decision to initiate prophylactic antithrombotic therapy should be done after a careful, individualized assessment of each patient's underlying risk factors.

2. Additional Bolded Warnings

You also request that FDA require Celgene to strengthen warnings about the risk of VTE and potential prophylactic measures throughout Thalomid's labeling. While you do not propose specific language, you specifically identify areas of the labeling in which you advocate including strengthened warnings. You propose strengthening the Warnings (Thrombotic Events) and Adverse Reactions sections, as well as the information under the heading "Other Adverse Events in the Published Literature or Reported from Other Sources." You also propose adding a new heading, "Other Adverse Events Observed in Cancer Patients," to the ADVERSE REACTIONS section (Petition at 11-12).

For the reasons discussed above, the Agency agrees that the labeling should be revised to reflect the relationship between thalidomide use and VTE, and the availability of prophylaxis. While we have not implemented all of the changes that you identify in your petition, overall, we believe that the new labeling includes far greater detail about the risks of and prophlaxis for VTE than you propose (Petition at 12).[12]

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[9] See Abdelkefi A., Torjman L., Ben Romdhane N., et al., 2005; Cavo M., Zamagni E., Tosi P., et al., 2005; Klueppelberg U., Shapira I., Chen L., et al., 2005; Weber D., Rankin K., Gavino M., et al., 2003.

[10] See Saif M.W., Allegra C.J., Greenberg B., 2001; Mozaffari E., Mupparapu M., Otis L., 2002; Spicka I., Rihova Z., Kvasnicka J., et al, 2003; Zangari M., Saghafifar F., Mehta P., et al., 2003.

[11] See, e.g., Harrison's Principles of Internal Medicine, Multiple Myeloma, 16th Ed. (2005) at 1621-1624.

[12] See New Labeling (enclosed with this response).

For instance, we decided against adding a new heading "Other Adverse Events Observed in Cancer Patients" in the ADVERSE REACTIONS section as you propose. Such a heading would be misleading because it would suggest that VTE occurs only among cancer patients treated with thalidomide and not among other patients treated with thalidomide -- a conclusion that we do not have data to support. Despite this decision, the WARNINGS section of the labeling has been revised to include warnings about the risk of VTE associated with thalidomide use and potential prophlaxis. Specifically, under WARNINGS (Thrombotic Events) the labeling now provides:

> The use of Thalomid® (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment (See **BOXED WARNINGS**).

Additionally, a heading entitled "Adverse Events in Multiple Myeloma Controlled Clinical Trial" has been added to the ADVERSE REACTIONS section. Under this heading is a chart identifying the most common treatment-emergent symptoms observed. Listed among the symptoms is "Thrombosis/embolism," with the corresponding frequency with which this condition was observed.

In sum, the labeling has been revised to address the concerns raised in your petition.

B. Initiation of a Phase IV Clinical Trial

You also request that FDA require Celgene to initiate a phase IV clinical study evaluating "the safety and efficacy of alternative thromboembolism prophylaxis regimens . . ." as well as "the safety and efficacy of reinitiating thalidomide-containing chemotherapy or corticosteroid regimens among cancer patients who develop a thromboembolic complication while receiving thalidomide-containing chemotherapy or corticosteroid regimens" (Petition at 12). While randomized studies to address these questions would be desirable, the Agency does not believe that they are feasible.

Within the past year, FDA has discussed the possibility of conducting a phase IV safety study of antithrombotic prophylaxis with physician-consultants from the Oncologic Drugs Advisory Committee who treat cancer patients with thalidomide. As a result of these consultations, we have identified several significant concerns with conducting this randomized phase IV safety study that you request. First, to be safe and ethical, a randomized trial of VTE prophylaxis during thalidomide therapy for multiple myeloma might need to exclude patients at high risk for VTE (i.e., those with a personal history of or genetic predisposition to VTE, and perhaps those receiving concurrent cytotoxic chemotherapy as well). Second, to be safe and ethical, the trial would also need to exclude patients at high risk for complications of anticoagulation (i.e., those with a history of falling, pathologic fracture, and bleeding). Third, evolving practice patterns suggest that some form of prophylaxis for high-risk patients has become commonplace. Fourth, as explained previously, some useful data already exist.[13] For these reasons, we are not comfortable recommending the randomized study of antithrombotic prophylaxis that you request.

FDA has also considered the possibility of requesting that the sponsor conduct a phase IV safety study of the reinitiation of thalidomide-containing chemotherapy or corticosteroid regimens among cancer patients who develop a thromboembolic complication while receiving thalidomide-containing chemotherapy or corticosteroid regimens. However, like the other phase IV study that you request, this study might need to exclude patients at high risk for VTE and at high risk for complications of anticoagulation. These exclusions would limit accrual to the study. Such a trial would also be difficult because the overall population of patients who develop a recurrent VTE while taking thalidomide is small. Moreover, the utility of any such trial is questionable because the results would be difficult to interpret given multiple myeloma patients' changing underlying risk factors for VTE over time.

Due to these considerations, the Agency has requested and Celgene has agreed to conduct a phase IV, non-randomized study that will address the issues that you have identified as important for further evaluation. Specifically, Celgene has agreed to conduct a prospective epidemiologic study of venous thrombotic events in thalidomide-treated multiple myeloma patients. Through enrollment of selected patients in the S.T.E.P.S. program, the study will collect additional information on use of VTE prophylaxis, incidence of initial VTEs, incidence of recurrent VTEs, and treatment of VTEs.

For all of the foregoing reasons, the Agency has decided that the specific phase IV studies that you request are not advisable at this time and that the phase IV commitment to which Celgene has agreed is a useful and workable alternative.

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[13] See *supra* at 5-6 (describing four recent studies in which preliminary uncontrolled data suggest that when prophylactic antithrombotic therapy is used in conjunction with thalidomide treatment, the potential for VTE is reduced).

C. Issuance of a "Dear Healthcare Professional" Letter

You also request that the Agency require Celgene to distribute a "Dear Healthcare Professional" letter to inform all prescribers of Thalomid in the United States about the risks of VTE when prescribing Thalomid in combination with other chemotherapy agents. For the reasons discussed in section II.A, the Agency agrees that such a letter is appropriate. Accordingly, the Agency has requested and Celgene has agreed to issue a "Dear Healthcare Professional" letter following today's approval.

D. Expansion of Thalomid's Risk Management Program

In your petition you state that "[t]he heightened potential for the development of a serious or life threatening DVT/PE[14] when a patient is prescribed Thalomid concomitant with chemotherapy agents warrants the expansion of the risk management goals for Thalomid to include the prevention or mitigation of DVT/PE" (Petition at 13). Specifically, you propose that at least three elements be added to the S.T.E.P.S. program: (1) The addition of a seventh risk group identified as cancer patients treated concomitantly with Thalomid and a chemotherapy agent; (2) the expansion of the Interactive Voice Response System survey to include the receipt of information relevant to identify the risk factors for DVT/PE; and (3) the mandatory reporting of any DVT/PE to Celgene and the FDA (Petition at 13).

The Agency does not believe that the addition of these elements to the S.T.E.P.S. program is advisable and, therefore, denies your request to amend the S.T.E.P.S. program. As an initial matter, the Agency has already obtained data from a trial specifically designed to collect information pertaining to the increased risk of venous thromboembolism that accompanies thalidomide use and has definitively determined that there was a statistically significant difference in the incidence of DVT and PE between the treatment arm and the comparator arm. In short, there is no question that thalidomide is associated with the development of DVT and PE; therefore, gathering additional information to further establish that association would not be worthwhile.

Moreover, the additional measures that you propose are likely to interfere with the accurate gathering and dispensing of information currently covered by the S.T.E.P.S. program and, thereby, interfere with the ability to prevent the serious teratogenic effects of thalidomide use. For instance, the S.T.E.P.S. program requires that, at the time of a patient's initial enrollment in S.T.E.P.S. and at the time that each thalidomide refill is dispensed, the dispensing pharmacist provide counseling about the safe use of thalidomide. This counseling is specifically designed to explain the risk of severe birth defects that accompanies fetal exposure to thalidomide and underscore the measures required to prevent pregnancy of females exposed to thalidomide directly or through a

[14] "DVT" is the abbreviation that you have used for "deep venous thrombosis" and "PE" is the abbreviation that you have used for "pulmonary embolism." DVT and PE are forms of venous thromboembolism, which we have abbreviated VTE throughout this response.

sexual partner. Requiring pharmacists to relay additional, unrelated information to patients is likely to make all of the information more difficult for pharmacists to articulate with accuracy and dilute the importance of the teratogenicity information being conveyed.

Finally, as discussed in sections II.A and II.C above, the risk of VTE associated with thalidomide use will be prominently displayed on the Thalomid labeling and distributed in a "Dear Healthcare Professional" letter -- measures that we believe are more than adequate to properly inform prescribing physicians and their patients.

III. CONCLUSION

As discussed in this response, we agree that the extant data suggest that thalidomide use in the treatment of multiple myeloma increases the risk of deep venous thrombosis and pulmonary embolus, and that this risk is further elevated by the use of thalidomide in combination with certain other cancer-treatment therapies. We also agree that there are data suggesting that prophylactic anticoagulants may lessen the risk of VTE in thalidomide-treated patients. Based on these data, your petition is granted in part and denied in part.

For the reasons articulated in sections II.A and II.C above, the Agency grants your requests to require Celgene to strengthen Thalomid's labeling to inform healthcare providers and patients about the relationship between thalidomide use and VTE events and the availability of prophylactic anticoagulants that may lessen the risk of those VTE events. In addition, Celgene has agreed to disseminate a "Dear Healthcare Professional" letter to underscore these points. For the reasons articulated in sections II.B. and II.D above, the Agency denies your requests to require Celgene to implement the two phase IV studies that you propose and to expand the S.T.E.P.S. program.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research

cc: Michael E. Cole, Esq.
Robert Deichert, Esq.

LIST OF REFERENCES

Abdelkefi A., Torjman L., Ben Romdhane N., et al., 2005, First-line thalidomide-dexamethasone therapy in preparation for autologous stem cell transplantation in young patients (<61 years) with symptomatic multiple myeloma, Bone Marrow Transplant, 36:193.

Anagnostopoulos A., Weber D., Rankin K., et al., 2003, Thalidomide and dexamethasone for resistant multiple myeloma, Br. J. Haematol., 121:768.

Arnulf B., Levy V., Leblond V., et al., 2003, Preliminary analysis of a double blind randomized study comparing thalidomide or placebo in combination with a VAD-like regimen in relapsing multiple myeloma, Hematol J., 4:S247 (abstr. 356).

Burley D., 1961, Is thalidomide to blame? Br. Med. J., 1:130.

Cavo M., Zamagni E., Tosi P., et al., March 10, 2005, Superiority of thalidomide and dexamethasone over vincristinedoxorubicin-dexamethasone as primary therapy in preparation for autologous transplantation for multiple myeloma, Blood, 2005, 106:35, E-pub.

Dimopoulos M.A., Zervas K., Kouvatseas G., et al., 2001, Thalidomide and dexamethasone combination for refractory multiple myeloma, Ann. Oncol., 12:991.

Fullerton P.M., Kremer M., 1961, Neuropathy after intake of thalidomide, Br. Med. J., 2:855-58.

Klueppelberg U., Shapira I., Chen L., et al., 2005, Long-term treatment of newly-diagnosed multiple myeloma with low-dose thalidomide, dexamethasone and zoledronate, Proc. Am. Soc. Clin. Oncol.(abstr. 6697).

Kropff M.H., Lang N., Bispin G., et al., 2003, Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (Hyper CDT) in primary refractory or relapsed multiple Myeloma, Br. J. Haematol., 122:607.

Kunz W., 1956, N-phthalyl-glutamin-saure-imid: esperimentelle untersuchungen an cinem neuen synthetischen produkt mi sedativen eigenenschaften, Arzneimittelforsch, 6:426-30.

Ludwig H., Drach J., Tóthová E., et al., 2005, Thalidomide-dexamethasone versus melphalan-prednisolone as first line treatment in elderly patients with multiple myeloma: an interim analysis, Proc. Am. Soc. Clin. Oncol. (abstr. 6537).

Mozaffari E., Mupparapu M., Otis L., 2002, Undiagnosed multiple myeloma causing extensive dental bleeding: Report of a case and a review, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endo., 94:448-53.

Osman K., Rajkumar S.V., 2001, Deep venous thrombosis and thalidomide therapy for multiple myeloma, N. Engl. J. Med., 344:1951.

Palumbo A., Bertola A., Musto P., et al., 2004, Oral melphalan, prednisone and thalidomide for newly diagnosed myeloma patients, Proc. Am. Soc. Clin. Oncol. (abstr. 6549).

Rajkumar S.V., Gertz M.A., Lacy M.Q., et al., 2003, Thalidomide as initial therapy for early-stage myeloma, Leukemia, 17:775.

Rajkumar S.V., Hayman S., Gertz M.A., et al., 2002, Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma, J. Clin. Oncol., 20:4319.

Saif M.W., Allegra C.J., Greenberg B., 2001, Bleeding diathesis in multiple myeloma, J. Hematother. Stem Cell Rsch., 10:657-60.

Schutt P., Ebeling P., Buttkereit U., et al., 2005, Thalidomide in combination with vincristine, eqirubicin and dexamethasone for previously untreated patients with multiple myeloma, Eur. J. Haematol., 4:40-6.

Sheskin J., 1965, Thalidomide in the treatment of lepra reactions, Clin. Pharmacol. Ther., 6:303-06.

Spicka I., Rihova Z., Kvasnicka J., et al, 2003, Disturbances of anticoagulation and fibrinolytic systems in monoclonal gammopathies - Another mechanism of M-protein interference with hemostasis, Thromb. Res., 112:297-300.

Wang M., Weber D.M., Delasalle K., et al., 2005, Thalidomide-dexamethasone as primary therapy for advanced multiple myeloma, Am. J. Hematol., 793:194.

Weber D., Rankin K., Gavino M., et al., 2003, Thalidomide alone or with dexamethasone for previously untreated, multiple myeloma, J. Clin. Oncol., 21:16.

Zangari M., Anaissie E., Barlogie B., et al., 2001, Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy, Blood, 98:1614.

Zangari M., Saghafifar F., Mehta P., et al., 2003, The blood coagulation mechanism in multiple myeloma, Semin. Thromb. Hemost., 29:275-82.

Zangari Z., Siegel E., Barlogie B., 2002, Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy, Blood, 100:1168.

Zervas K., Dimopoulas M.A., Hatziharissi E., et al., 2003, A phase II study on efficacy and tolerability of combination chemotherapy with VAD regimen containing liposomal doxorubicin and thalidomide in newly diagnosed multiple myeloma patients, Hematol. J., 4:S243 (abstr. 347).

PROPOSED CHANGES TO APPROVED THALOMID® PACKAGE INSERT
Highlighted Version

THALOMID® (thalidomide) Capsules 50 mg, 100 mg, & 200mg

WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.

IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY. THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg, 100 mg or 200 mg)] TAKEN BY A PREGNANT WOMAN DURING HER PREGNANCY CAN CAUSE SEVERE BIRTH DEFECTS.

BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE CHANCE OF FETAL EXPOSURE TO THALOMID® (thalidomide) AS NEGLIGIBLE AS POSSIBLE, THALOMID® (thalidomide) IS APPROVED FOR MARKETING ONLY UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAM APPROVED BY THE FOOD AND DRUG ADMINISTRATION. THIS PROGRAM IS CALLED THE "SYSTEM FOR THALIDOMIDE EDUCATION AND PRESCRIBING SAFETY (*S.T.E.P.S.* ®)."

UNDER THIS RESTRICTED DISTRIBUTION PROGRAM, ONLY PRESCRIBERS AND PHARMACISTS REGISTERED WITH THE PROGRAM ARE ALLOWED TO PRESCRIBE AND DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUIREMENTS OF THE *S.T.E.P.S.* ® PROGRAM IN ORDER TO RECEIVE PRODUCT.

PLEASE SEE THE FOLLOWING BOXED WARNINGS CONTAINING SPECIAL INFORMATION FOR PRESCRIBERS, FEMALE PATIENTS, AND MALE PATIENTS ABOUT THIS RESTRICTED DISTRIBUTION PROGRAM.

PRESCRIBERS

THALOMID® (thalidomide) may be prescribed only by licensed prescribers who are registered in the *S.T.E.P.S.* ® program and understand the risk of teratogenicity if thalidomide is used during pregnancy.

Major human fetal abnormalities related to thalidomide administration during pregnancy have been documented: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented.[1] Mortality at or shortly after birth has been reported at about 40%.[2]

Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 4 weeks before beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks following discontinuation of thalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because the patient has been postmenopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from heterosexual sexual contact is the chosen method. Women of childbearing potential should be referred to a qualified provider of contraceptive methods, if needed. Sexually mature women who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

Before starting treatment, women of childbearing potential should have a pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning thalidomide therapy. A prescription for thalidomide for a woman of childbearing potential must not be issued by the prescriber until a written report of a negative pregnancy test has been obtained by the prescriber.

Male Patients: Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential even if he has undergone a successful vasectomy.

Once treatment has started, pregnancy testing should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated at 4 weeks in women with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

If pregnancy does occur during thalidomide treatment, thalidomide must be discontinued immediately.

Any suspected fetal exposure to THALOMID® (thalidomide) must be reported immediately to the FDA *via* the MedWatch number at 1-800-FDA-1088 and also to Celgene Corporation. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

FEMALE PATIENTS

Thalidomide is contraindicated in WOMEN of childbearing potential unless alternative therapies are considered inappropriate AND the patient MEETS ALL OF THE FOLLOWING CONDITIONS (i.e., she is essentially unable to become pregnant while on thalidomide therapy):

- she understands and can reliably carry out instructions
- she is capable of complying with the mandatory contraceptive measures, pregnancy testing, patient registration, and patient survey as described in the

System for Thalidomide Education and Prescribing Safety (*S.T.E.P.S.* ®) program.

- she has received both oral and written warnings of the hazards of taking thalidomide during pregnancy and of exposing a fetus to the drug.
- she has received both oral and written warnings of the risk of possible contraception failure and of the need to use two reliable forms of contraception simultaneously (see **CONTRAINDICATIONS**), unless continuous abstinence from heterosexual sexual contact is the chosen method. Sexually mature women who have not undergone a hysterectomy or who have not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at some time in the preceding 24 consecutive months) are considered to be women of childbearing potential.
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for 4 weeks prior to beginning thalidomide therapy, during thalidomide therapy, and for 4 weeks after discontinuation of thalidomide therapy.
- she has had a negative pregnancy test with a sensitivity of at least 50 mIU/mL, within the 24 hours prior to beginning therapy. (See **PRECAUTIONS, CONTRAINDICATIONS**.)
- if the patient is between 12 and 18 years of age, her parent or legal guardian must have read this material and agreed to ensure compliance with the above.

MALE PATIENTS

Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- he understands and can reliably carry out instructions.
- he is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the *S.T.E.P.S.* ® program.
- he has received both oral and written warnings of the hazards of taking thalidomide and exposing a fetus to the drug.
- he has received both oral and written warnings of the risk of possible contraception failure and of the presence of thalidomide in semen. He has been instructed that he must always use a latex condom during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy.
- he acknowledges, in writing, his understanding of these warnings and of the need to use a latex condom during any sexual contact with women of childbearing potential, even if he has undergone a successful vasectomy. Sexually mature women who have not undergone a hysterectomy or who have

not been postmenopausal for at least 24 consecutive months (i.e., who have had menses at any time in the preceding 24 consecutive months) are considered to be women of childbearing potential.

- if the patient is between 12 and 18 years of age, his parent or legal guardian must have read this material and agreed to ensure compliance with the above.

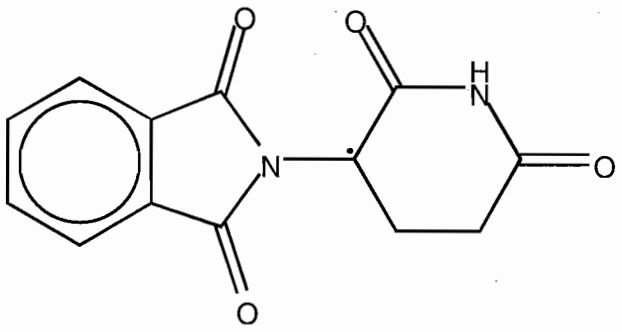
Venous Thromboembolic Events

The use of Thalomid® (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

DESCRIPTION

THALOMID® (thalidomide), α-(N-phthalimido) glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide is $C_{13}H_{10}N_2O_4$ and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1.

Chemical Structure of thalidomide



Note: • = asymmetric carbon atom

Thalidomide is an off-white to white, odorless, crystalline powder that is soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S-(-) or R-(+). THALOMID® (thalidomide) is an

equal mixture of the S-(-) and R-(+) forms and, therefore, has a net optical rotation of zero.

THALOMID® (thalidomide) is available in 50 mg, 100 mg and 200 mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: pregelatinized starch and magnesium stearate. The 50 mg capsule shell contains gelatin, titanium dioxide, and black ink. The 100 mg capsule shell contains black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black ink. The 200 mg capsule shell contains FD&C blue #2, titanium dioxide, gelatin, and white ink.

CLINICAL PHARMACOLOGY

Mechanism of Action

The mechanism of action of thalidomide is not fully understood. Thalidomide possesses immunomodulatory, anti-inflammatory and anti-angiogenic properties. Available data from in vitro studies and clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor-alpha (TNF-α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration.[3-6] For example, administration of thalidomide has been reported to decrease circulating levels of TNF-α in patients with erythema nodosum leprosum (ENL)[3], however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients.[7] Other anti-inflammatory and immunomodulatory properties of thalidomide may include suppression of macrophage involvement in prostaglandin synthesis, and modulation of interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. Thalidomide treatment of multiple myeloma patients is accompanied by an increase in the number of circulating natural killer cells, and an increase in plasma levels of interleukin-2 and interferon-gamma (T cell-derived cytokines associated with cytotoxic activity). Thalidomide was found to inhibit angiogenesis in a human umbilical artery explant model *in vitro*. The cellular processes of angiogenesis inhibited by thalidomide may include the proliferation of endothelial cells.

Pharmacokinetics and Drug Metabolism

Absorption

The absolute bioavailability of thalidomide from THALOMID® (thalidomide) capsules has not yet been characterized in human subjects due to its poor aqueous solubility. However, the capsules are 90% bioavailable relative to an oral PEG solution. In studies of both healthy volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations (T_{max}) of THALOMID® (thalidomide) ranged from 2.9 to 5.7 hours indicating that THALOMID® (thalidomide) is slowly absorbed from the gastrointestinal tract. While the extent of absorption (as measured by area under the curve [AUC]) is proportional to dose in healthy subjects, the observed peak concentration (C_{max}) increased in a less than proportional manner (see Table 1 below). This lack of C_{max} dose proportionality, coupled with the observed increase in T_{max}

values, suggests that the poor solubility of thalidomide in aqueous media may be hindering the rate of absorption.

Table 1
Pharmacokinetic Parameter Values for THALOMID® (thalidomide)
Mean (%CV)

Population/ Single Dose	$AUC_{0\infty}$ µg•hr/mL	C_{max} µg/mL	T_{max} (hrs)	Half-life (hrs)
Healthy Subjects (n=14)				
50 mg	4.9 (16%)	0.62 (52%)	2.9 (66%)	5.52 (37%)
200 mg	18.9 (17%)	1.76 (30%)	3.5 (57%)	5.53 (25%)
400 mg	36.4 (26%)	2.82 (28%)	4.3 (37%)	7.29 (36%)
Patients with Hansen's Disease (n=6)				
400 mg	46.4 (44.1%)	3.44 (52.6%)	5.7 (27%)	6.86 (17%)

Coadministration of THALOMID® (thalidomide) with a high fat meal causes minor (<10%) changes in the observed AUC and C_{max} values; however, it causes an increase in T_{max} to approximately 6 hours.

Distribution

In human blood plasma, the geometric mean plasma protein binding was 55% and 66%, respectively, for (+)-(R)- and (-)-(S)-thalidomide.[8] In a pharmacokinetic study of thalidomide in HIV-seropositive adult male subjects receiving thalidomide 100 mg/day, thalidomide was detectable in the semen.

Metabolism

At the present time, the exact metabolic route and fate of thalidomide is not known in humans. Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple products. In a repeat dose study in which THALOMID® (thalidomide) 200 mg was administered to 10 healthy females for 18 days, thalidomide displayed similar pharmacokinetic profiles on the first and last day of dosing. This suggests that thalidomide does not induce or inhibit its own metabolism.

Elimination

As indicated in Table 1 (above) the mean half-life of elimination ranges from approximately 5 to 7 hours following a single dose and is not altered upon multiple dosing. As noted in the metabolism subsection, the precise metabolic fate and route of elimination of thalidomide in humans is not known at this time. Thalidomide itself has a renal clearance of 1.15 mL/minute with less than 0.7% of the dose excreted in the urine as unchanged drug. Following a single dose, urinary levels of thalidomide were undetectable 48 hrs after dosing. Although thalidomide is thought to be hydrolyzed to a number of metabolites[9] only a very small amount (0.02% of the administered dose) of 4-OH-thalidomide was identified in the urine of subjects 12 to 24 hours after dosing.

Pharmacokinetic Data in Special Populations

HIV-seropositive Subjects: There is no apparent significant difference in measured pharmacokinetic parameter values between healthy human subjects and HIV-seropositive subjects following single dose administration of THALOMID® (thalidomide) capsules.

Patients with Hansen's Disease: Analysis of data from a small study in Hansen's patients suggests that these patients, relative to healthy subjects, may have an increased bioavailability of THALOMID® (thalidomide). The increase is reflected both in an increased area under the curve and in increased peak plasma levels. The clinical significance of this increase is unknown.

Patients with Renal Insufficiency: The pharmacokinetics of thalidomide in patients with renal impairment have not been determined. In a study of 6 patients with end-stage renal disease, thalidomide (200 mg/day) was administered on a non-dialysis day and on a dialysis day. Comparison of concentration-time profiles on a non-dialysis day and during dialysis where blood samples were collected at least 10 hours following the dose, showed that the mean total clearance increased by a factor of 2.5 during hemodialysis. Because the dialysis was performed 10 hours following administration of the dose, the drug-concentration time curves were not statistically significantly different for days patients were on and off of dialysis. Thus, no dosage adjustment is needed for renally-impaired patients on dialysis.

Patients with Hepatic Disease: The pharmacokinetics of thalidomide in patients with hepatic impairment have not been determined.

Age: Analysis of the data from pharmacokinetic studies in healthy volunteers and patients with Hansen's disease ranging in age from 20 to 69 years does not reveal any age-related changes.

Pediatric: No pharmacokinetic data are available in subjects below the age of 18 years.

Gender: While a comparative trial of the effects of gender on thalidomide pharmacokinetics has not been conducted, examination of the data for thalidomide does not reveal any significant gender differences in pharmacokinetic parameter values.

Race: Pharmacokinetic differences due to race have not been studied.

Clinical Studies

Clinical Study in Multiple Myeloma:

The efficacy of THALOMID® in multiple myeloma was demonstrated in a randomized, multi-center open-label study of 207 newly diagnosed patients. This study randomized symptomatic patients with newly diagnosed multiple myeloma to THALOMID® plus dexamethasone (Thal + Dex; N = 103) versus dexamethasone alone (Dex alone; N=104). The THALOMID dose was 200 mg daily and the dexamethasone dose was 40 mg orally once daily on days 1-4, 9-12, and 17-20 every 28-days. Each group was treated for four 28-day cycles.

Baseline demographic and disease characteristics for the study population are summarized in Tables 2 and 3 respectively.

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Table 2 Baseline Patient Demographics		
Characteristic	**Thal + Dex (N=103)**	**Dex alone (N=104)**
Age (years)		
Median	65	68
Range	37 – 83	38 – 83
Gender[1]		
Male	53 (51%)	61 (59%)
Female	50 (49%)	42 (40%)
Race[2]		
Caucasian	90 (87%)	90 (87%)
Black	11 (11%)	11 (11%)
Other	1 (1%)	2 (2%)

279 [1]Missing information for 1 patient in the Dex alone group
280 [2]Missing information for 1 patient per arm
281
282

Table 3 Baseline Disease Characteristics		
Characteristic	**Thal + Dex (N=103)**	**Dex alone (N=104)**
Stage (Durie-Salmon), N (%)[1]		
I	14 (13.6%)	17 (16.3%)
II	47 (45.6%)	44 (42.3%)
III	41 (39.8%)	43 (41.3%)
Immunoglobulin Type, N (%)[2]		
IgA	21 (20.4%)	22 (21.2%)
IgG	63 (61.2%)	60 (57.7%)
IgM	0 (0.0%)	1 (1.0%)
Biclonal	0 (0.0%)	1 (1.0%)
Lytic Lesions[3]		
None	28 (27.1%)	14 (13.5%)
1-3 lesions	24 (23.3%)	19 (18.3%)
>3 lesions	34 (33.0%)	41 (39.4%)
Serum Light Chain[4]		
Kappa	59 (57.3%)	53 (51.0%)
Lambda	28 (27.2%)	40 (38.5%)

283 [1]Missing information for 1 patient in Thal + Dex arm
284 [2]Missing information for 19 patients in Thal + Dex arm and 20 patients in Dex alone arm
285 [3]Missing information for 17 patients in Thal + Dex arm and 30 patients in Dex alone arm
286 [4]Missing information for 16 patients in Thal + Dex arm and 11 patients in Dex
287 alone arm

288 Response rate was the primary endpoint. Response rates based on serum or urine
289 paraprotein measurements were significantly higher in the combination arm (51.5 %
290 compared with 35.6 % for dexamethasone alone).

291 **Erythema Nodosum Leprosum (ENL)**

The primary data demonstrating the efficacy of thalidomide in the treatment of the cutaneous manifestations of moderate to severe ENL are derived from the published medical literature and from a retrospective study of 102 patients treated by the U.S. Public Health Service.

Two double-blind, randomized, controlled trials reported the dermatologic response to a 7-day course of 100 mg thalidomide (four times daily) or control. Dosage was lower for patients under 50 kg in weight.

Table 4
Double-Blind, Controlled Clinical Trials of Thalidomide in Patients with ENL: Cutaneous Response

Reference	No. of Patients	No. Treatment Courses*	Percent Responding**	
Iyer *et al.*[10]			Thalidomide	Aspirin
Bull World Health Organization 1971;45:719	92	204	75%	25%
Sheskin *et al.*[11]			Thalidomide	Placebo
Int J Lep 1969;37:135	52	173	66%	10%

*In patients with cutaneous lesions
**Iyer: Complete response or lesions absent
**Sheskin: Complete improvement + "striking" improvement (i.e., >50% improvement)

Waters[12] reported the results of two studies, both double-blind, randomized, placebo-controlled, crossover trials in a total of 10 hospitalized, steroid-dependent patients with chronic ENL treated with 100 mg thalidomide or placebo (three times daily). All patients also received dapsone. The primary endpoint was reduction in weekly steroid dosage.

Table 5
Double Blind, Controlled Trial of Thalidomide in Patients with ENL: Reduction in Steroid Dosage

Reference	Duration of Treatment	No. of Patients	Number Responding	
			Thalidomide	Placebo
Waters[12]	4 weeks	9	4/5	0/4
Lep Rev 1971;42:26	6 weeks (crossover)	8	8/8	1/8

Data on the efficacy of thalidomide in prevention of ENL relapse were derived from a retrospective evaluation of 102 patients treated under the auspices of the U.S. Public Health Service. A subset of patients with ENL controlled on thalidomide demonstrated repeated relapse upon drug withdrawal and remission with reinstitution of therapy.

Twenty U.S. patients between the ages of 11 and 17 years were treated with thalidomide, generally at 100 mg daily. Response rates and safety profiles were similar to that observed in the adult population.

Thirty-two other published studies containing over 1600 patients consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL with thalidomide.

INDICATIONS AND USAGE

Multiple Myeloma

THALOMID® (thalidomide) in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma.

The effectiveness of THALOMID® is based on response rates (**see CLINICAL STUDIES section**). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

Erythema Nodosum Leprosum

THALOMID® (thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL).

THALOMID® (thalidomide) is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis.

THALOMID® (thalidomide) is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

CONTRAINDICATIONS (See BOXED WARNINGS.)

Pregnancy: Category X

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See **BOXED WARNINGS**.) When there is no alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Women must commit either to abstain continuously from heterosexual sexual contact or to use two methods of reliable birth control, including at least one highly effective method (e.g., IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with thalidomide, during therapy with thalidomide, and continuing for 4 weeks following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically contraindicated (see also **PRECAUTIONS: Drug Interactions**), two other effective or highly effective methods may be used.

Women of childbearing potential being treated with thalidomide should have a pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning thalidomide therapy and then weekly during the first 4 weeks of thalidomide therapy, then at 4 week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs during thalidomide treatment, thalidomide must be discontinued immediately. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with

women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

THALOMID® (thalidomide) is contraindicated in patients who have demonstrated hypersensitivity to the drug and its components.

WARNINGS (See BOXED WARNINGS.)

Birth Defects:

Thalidomide can cause severe birth defects in humans. (See **BOXED WARNINGS** and **CONTRAINDICATIONS**.) Patients should be instructed to take thalidomide only as prescribed and not to share their thalidomide with anyone else. Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

Thrombotic Events:

The use of Thalomid® (thalidomide) in multiple myeloma results in an increased risk of venous thromboembolic events, such as deep venous thrombosis and pulmonary embolus. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment (See **BOXED WARNINGS**).

Drowsiness and Somnolence:

Thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.

Peripheral Neuropathy:

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months; however, reports following relatively short-term use also exist. The correlation with cumulative dose is unclear. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all.

Few reports of neuropathy have arisen in the treatment of ENL despite long-term thalidomide treatment. However, the inability clinically to differentiate thalidomide neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to determine accurately the incidence of thalidomide-related neuropathy in ENL patients treated with thalidomide.

Patients should be examined at monthly intervals for the first 3 months of thalidomide therapy to enable the clinician to detect early signs of neuropathy, which include numbness, tingling or pain in the hands and feet. Patients should be evaluated periodically thereafter during treatment. Patients should be regularly counseled, questioned, and evaluated for signs or symptoms of peripheral neuropathy. Consideration should be given to electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baseline and thereafter every 6 months in an effort to detect asymptomatic neuropathy. If symptoms of drug-induced neuropathy develop, thalidomide should be discontinued immediately to limit further damage, if clinically appropriate. Usually, treatment with thalidomide should only be reinitiated if the neuropathy returns to baseline status. Medications known to be associated with neuropathy should be used with caution in patients receiving thalidomide.

Dizziness and Orthostatic Hypotension:

Patients should also be advised that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

Neutropenia:

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of thalidomide. Treatment should not be initiated with an absolute neutrophil count (ANC) of $<750/mm^3$. White blood cell count and differential should be monitored on an ongoing basis, especially in patients who may be more prone to neutropenia, such as patients who are HIV-seropositive. If ANC decreases to below $750/mm^3$ while on treatment, the patient's medication regimen should be re-evaluated and, if the neutropenia persists, consideration should be given to withholding thalidomide if clinically appropriate.

Increased HIV Viral Load:

In a randomized, placebo controlled trial of thalidomide in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase (median change = 0.42 $\log_{10}$ copies HIV RNA/mL, p = 0.04 compared to placebo).[7] A similar trend was observed in a second, unpublished study conducted in patients who were HIV-seropositive.[13]The clinical significance of this increase is unknown. Both studies were conducted prior to availability of highly active antiretroviral therapy. Until the clinical significance of this finding is further understood, in HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.

PRECAUTIONS

General:

The only type of thalidomide exposure known to result in drug associated birth defects are as a result of direct oral ingestion of thalidomide. Currently no specific data are available regarding the cutaneous absorption or inhalation of thalidomide in women of child-bearing potential and whether these exposures may result in any birth defects. Patients should be instructed to not extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion. If there is contact with non-intact thalidomide capsules or the powder contents, the exposed area should be washed with soap and water.

Thalidomide has been shown to be present in the serum and semen of patients receiving thalidomide. If healthcare providers or other care givers are exposed to body fluids from patients receiving THALOMID® (thalidomide), appropriate precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to THALOMID® (thalidomide) or the exposed area should be washed with soap and water.

Hypersensitivity:

Hypersensitivity to THALOMID® (thalidomide) has been reported. Signs and symptoms have included the occurrence of erythematous macular rash, possibly associated with fever, tachycardia, and hypotension, and if severe, may necessitate interruption of therapy. If the reaction recurs when dosing is resumed, THALOMID® (thalidomide) should be discontinued.

Bradycardia:

Bradycardia in association with thalidomide use has been reported. Cases of bradycardia have been reported, some required medical interventions. The clinical significance and underlying etiology of the bradycardia noted in some thalidomide-treated patients are presently unknown.

Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis:

Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, which may be fatal, have been reported. THALOMID® (thalidomide) should be discontinued if a skin rash occurs and only resumed following appropriate clinical evaluation. If the rash is exfoliative, purpuric, or bullous or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of THALOMID® (thalidomide) should not be resumed.

Seizures:

Although not reported from pre-marketing controlled clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of THALOMID® (thalidomide) in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence. During therapy with thalidomide, patients with a history of seizures or with other risk factors for the

development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity.

Information for Patients (See BOXED WARNINGS.)

Patients should be instructed about the potential teratogenicity of thalidomide and the precautions that must be taken to preclude fetal exposure as per the *S.T.E.P.S.* ® program and boxed warnings in this package insert. Patients should be instructed to take thalidomide only as prescribed in compliance with all of the provisions of the *S.T.E.P.S.* ® Restricted Distribution Program.

Patients should be instructed to not extensively handle or open THALOMID® (thalidomide) Capsules and to maintain storage of capsules in blister packs until ingestion.

Patients should be instructed not to share medication with anyone else.

Patients should be instructed that thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex machinery. Patients should be instructed that thalidomide may potentiate the somnolence caused by alcohol.

Patients should be instructed that thalidomide can cause peripheral neuropathies that may be initially signaled by numbness, tingling, or pain or a burning sensation in the feet or hands. Patients should be instructed to report such occurrences to their prescriber immediately.

Patients should also be instructed that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

Patients should be instructed that they are not permitted to donate blood while taking thalidomide. In addition, male patients should be instructed that they are not permitted to donate sperm while taking thalidomide.

Patients should be educated about the signs and symptoms of thromboembolism and instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

514 **Laboratory Tests**

515 ***Pregnancy Testing:*** **(See BOXED WARNINGS.)** Women of childbearing potential
516 should have a pregnancy test performed (sensitivity of at least 50 mIU/mL). The test
517 should be performed within the 24 hours prior to beginning thalidomide therapy and
518 then weekly during the first 4 weeks of use, then at 4 week intervals in women with
519 regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.
520 Pregnancy testing and counseling should be performed if a patient misses her period or
521 if there is any abnormality in menstrual bleeding.

522 ***Neutropenia:*** **(See WARNINGS.)**

523 ***Increased HIV Viral Load: (See WARNINGS.)***

524 **Drug Interactions**

525 Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol,
526 chlorpromazine, and reserpine.

527 ***Peripheral Neuropathy:*** Medications known to be associated with peripheral
528 neuropathy should be used with caution in patients receiving thalidomide.

529 ***Oral Contraceptives:*** In 10 healthy women, the pharmacokinetic profiles of
530 norethindrone and ethinyl estradiol following administration of a single dose containing
531 1.0 mg of norethindrone acetate and 75 μg of ethinyl estradiol were studied. The results
532 were similar with and without coadministration of thalidomide 200 mg/day to steady-
533 state levels.

534 **Important Non-Thalidomide Drug Interactions**

535 ***Drugs That Interfere with Hormonal Contraceptives:*** Concomitant use of HIV-
536 protease inhibitors, griseofulvin, modafinil, pencillins, rifampin, rifabutin, phenytoin,
537 carbamazepine, or certain herbal supplements such as St. John's Wort with hormonal
538 contraceptive agents may reduce the effectiveness of the contraception and up to one
539 month after discontinuation of these concomitant therapies. Therefore, women requiring
540 treatment with one or more of these drugs must use two OTHER effective or highly
541 effective methods of contraception or abstain from heterosexual sexual contact while
542 taking thalidomide.

543 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

544 Two-year carcinogenicity studies were conducted in male and female rats and mice. No
545 compound-related tumorigenic effects were observed at the highest dose levels of 3,000
546 mg/kg/day to male and female mice (38-fold greater than the highest recommended
547 daily human dose of 400 mg based upon body surface area [BSA]), 3,000 mg/kg/day to
548 female rats (75-fold the maximum human dose based upon BSA), and 300 mg/kg/day to
549 male rats (7.5-fold the maximum human dose based upon BSA).

550 Thalidomide was neither mutagenic nor genotoxic in the following assays: the Ames
551 bacterial (S. typhimurium and E. coli) reverse mutation assay, a Chinese hamster ovary
552 cell (AS52/XPRT) forward mutation assay, and an *in vivo* mouse micronucleus test.

Fertility studies were conducted in male and female rabbits; no compound-related effects in mating and fertility indices were observed at any oral thalidomide dose level including the highest of 100 mg/kg/day to female rabbits and 500 mg/kg/day to male rabbits (approximately 5- and 25-fold the maximum human dose, respectively, based upon BSA). Testicular pathological and histopathological effects (classified as slight) were seen in male rabbits at dose levels ≥ 30 mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA).

Pregnancy

Pregnancy Category X (See BOXED WARNING and CONTRAINDICATIONS.)

Because of the known human teratogenicity of thalidomide, thalidomide is contraindicated in women who are or may become pregnant and who are not using the two required types of birth control or who are not continually abstaining from heterosexual sexual contact. If thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug. Even a single dose [1 capsule (50 mg, 100 mg, or a 200 mg)] taken by a pregnant woman can cause birth defects. If pregnancy does occur during treatment, the drug should be immediately discontinued. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to THALOMID® (thalidomide) must be reported to the FDA *via* the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

A pre- and postnatal reproductive toxicity study was conducted in pregnant female rabbits. Compound-related increased abortion incidences and elevated fetotoxicity were observed at the lowest oral dose level of 30 mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA) and all higher dose levels. Neonatal mortality was elevated at oral dose levels to the lactating female rabbits ≥ 150 mg/kg/day (approximately 7.5-fold the maximum human dose based upon BSA). No delay in postnatal development, including learning and memory functions, were noted at the oral dose level to the lactating female rabbits of 150 mg/kg/day (average thalidomide concentrations in milk ranged from 22 to 36 μg/ml).

Use in Nursing Mothers

It is not known whether thalidomide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from thalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use

Of the total number of subjects in this clinical study of thalidomide and dexamethasone combination, 50% were 65 and over, while 15% were 75 and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The most serious toxicity associated with thalidomide is its documented human teratogenicity. (See **BOXED WARNINGS** and **CONTRAINDICATIONS.**) The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy. The critical period is estimated, depending on the source of information, to range from 35 to 50 days after the last menstrual period. The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant. Based on present knowledge, thalidomide must not be used at any time during pregnancy.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential.

Thalidomide is associated with drowsiness/somnolence, peripheral neuropathy, dizziness/orthostatic hypotension, neutropenia, and HIV viral load increase. (See **WARNINGS**.)

Hypersensitivity to THALOMID® (thalidomide) and bradycardia in patients treated with thalidomide have been reported. (See **PRECAUTIONS**.)

Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide. Thalidomide has been studied in controlled and uncontrolled clinical trials in patients with multiple myeloma and ENL and in people who are HIV-seropositive. In addition, thalidomide has been administered investigationally for more than 20 years in numerous indications. Adverse event profiles from these uses are summarized in the sections that follow.

Other Adverse Events

Due to the nature of the longitudinal data that form the basis of this product's safety evaluation, no determination has been made of the causal relationship between the reported adverse events listed below and thalidomide. These lists are of various adverse events noted by investigators in patients to whom they had administered thalidomide under various conditions. The use of thalidomide may not limit disease progression and/or death.

Adverse events in Multiple Myeloma Controlled Clinical Trial

The safety analysis was conducted on 204 patients who received study drug in the randomized trial. Table 6 lists the most common treatment – emergent signs and symptoms (occurring at ≥ 10%) that were observed. The most frequently reported adverse events were constipation, sensory neuropathy, confusion, hypocalcemia, edema, dyspnea, thrombosis/embolism, and rash/desquamation (occurring in ≥20% of patients and with a frequency of ≥10% in patients treated with Thalomid®/dexamethasone compared with dexamethasone alone).

Twenty-three percent of patients (47/204) discontinued due to adverse events; thirty percent (31/102) from the Thalomid®/dexamethasone arm and sixteen percent (16/102) from the dexamethasone alone arm.

Table 6
Treatment-Emergent Adverse Events in ≥ 10% of All Patients
Adverse Event (Safety Population; N=204)

Organ System Class/Preferred Term	Thal + Dex (N=102)			Dex Alone (N=102)		
	All Events [n,(%)]	Grade 3 Events [n,(%)]	Grade 4 Events [n,(%)]	All Events [n,(%)]	Grade 3 Events [n,(%)]	Grade 4 Events [n,(%)]
Metabolic/Laboratory	97 (95.1)	30 (29.4)	15 (14.7)	96 (94.1)	28 (27.5)	6 (5.9)
Hyperglycemia	74 (72.5)	12 (11.8)	4 (3.9)	81 (79.4)	17 (16.7)	2 (2.0)
Hypocalcemia	73 (71.6)	9 (8.8)	6 (5.9)	60 (58.8)	4 (3.9)	1 (1.0)
Hyponatremia	44 (43.1)	11 (10.8)	2 (2.0)	49 (48.0)	13 (12.7)	2 (2.0)
Hypokalemia	23 (22.5)	4 (3.9)	1 (1.0)	23 (22.5)	0 (0.0)	1 (1.0)
Hyperkalemia	19 (18.6)	1 (1.0)	2 (2.0)	20 (19.6)	2 (2.0)	0 (0.0)
Neurology	92 (90.2)	27 (26.5)	5 (4.9)	76 (74.5)	15 (14.7)	4 (3.9)
Neuropathy-sensory	55 (53.9)	3 (2.9)	1 (1.0)	28 (27.5)	1 (1.0)	0 (0.0)
Confusion	29 (28.4)	6 (5.9)	3 (2.9)	12 (11.8)	2 (2.0)	3 (2.9)
Anxiety / agitation	26 (25.5)	1 (1.0)	0 (0.0)	14 (13.7)	3 (2.9)	0 (0.0)
Tremor	26 (25.5)	1 (1.0)	0 (0.0)	6 (5.9)	0 (0.0)	0 (0.0)
Insomnia	23 (22.5)	0 (0.0)	0 (0.0)	48 (47.1)	5 (4.9)	0 (0.0)
Depression	22 (21.6)	2 (2.0)	0 (0.0)	24 (23.5)	1 (1.0)	0 (0.0)
Neuropathy-motor	22 (21.6)	7 (6.9)	1 (1.0)	16 (15.7)	5 (4.9)	1 (1.0)
Dizziness / lightheadedness	20 (19.6)	1 (1.0)	0 (0.0)	14 (13.7)	0 (0.0)	0 (0.0)
Constitutional Symptoms	91 (89.2)	17 (16.7)	3 (2.9)	84 (82.4)	15 (14.7)	2 (2.0)
Fatigue	81 (79.4)	14 (13.7)	3 (2.9)	72 (70.6)	12 (11.8)	2 (2.0)
Fever	24 (23.5)	1 (1.0)	0 (0.0)	20 (19.6)	3 (2.9)	0 (0.0)
Weight loss	23 (22.5)	1 (1.0)	0 (0.0)	21 (20.6)	2 (2.0)	0 (0.0)
Weight gain	22 (21.6)	1 (1.0)	0 (0.0)	13 (12.7)	0 (0.0)	0 (0.0)
Blood/Bone Marrow	88 (86.3)	25 (24.5)	9 (8.8)	96 (94.1)	10 (9.8)	10 (9.8)
Hemoglobin (decreased)	79 (77.5)	13 (12.7)	3 (2.9)	88 (86.3)	5 (4.9)	1 (1.0)
Leukocytes (decreased)	36 (35.3)	6 (5.9)	1 (1.0)	30 (29.4)	1 (1.0)	2 (2.0)
Neutrophils (decreased)	32 (31.4)	8 (7.8)	5 (4.9)	24 (23.5)	3 (2.9)	8 (7.8)
Platelets (decreased)	24 (23.5)	2 (2.0)	2 (2.0)	34 (33.3)	3 (2.9)	0 (0.0)
Gastrointestinal	83 (81.4)	19 (18.6)	3 (2.9)	70 (68.6)	8 (7.8)	0 (0.0)

Constipation	56 (54.9)	8 (7.8)	0 (0.0)	29 (28.4)	1 (1.0)	0 (0.0)
Anorexia	29 (28.4)	4 (3.9)	0 (0.0)	25 (24.5)	2 (2.0)	0 (0.0)
Nausea	29 (28.4)	5 (4.9)	0 (0.0)	23 (22.5)	1 (1.0)	0 (0.0)
Vomiting	12 (11.8)	2 (2.0)	0 (0.0)	12 (11.8)	1 (1.0)	0 (0.0)
Diarrhea	12 (11.8)	1 (1.0)	0 (0.0)	17 (16.7)	3 (2.9)	0 (0.0)
Dyspepsia	8 (7.8)	1 (1.0)	0 (0.0)	19 (18.6)	1 (1.0)	0 (0.0)
Cardiovascular	70 (68.6)	24 (23.5)	14 (13.7)	60 (58.8)	17 (16.7)	5 (4.9)
Edema	58 (56.9)	6 (5.9)	0 (0.0)	47 (46.1)	4 (3.9)	0 (0.0)
Thrombosis/embolism	23 (22.5)	13 (12.7)	9 (8.8)	5 (4.9)	3 (2.9)	2 (2.0)
Hypotension	16 (15.7)	7 (6.9)	2 (2.0)	15 (14.7)	2 (2.0)	3 (2.9)
Hypertension	11 (10.8)	1 (1.0)	0 (0.0)	12 (11.8)	9 (8.8)	0 (0.0)
Pain	64 (62.7)	8 (7.8)	2 (2.0)	66 (64.7)	15 (14.7)	0 (0.0)
Bone pain	31 (30.4)	3 (2.9)	2 (2.0)	37 (36.3)	11 (10.8)	0 (0.0)
Pain-other	25 (24.5)	4 (3.9)	0 (0.0)	26 (25.5)	3 (2.9)	0 (0.0)
Headache	20 (19.6)	3 (2.9)	0 (0.0)	23 (22.5)	0 (0.0)	0 (0.0)
Myalgia	17 (16.7)	0 (0.0)	0 (0.0)	14 (13.7)	1 (1.0)	0 (0.0)
Arthralgia	13 (12.7)	0 (0.0)	0 (0.0)	10 (9.8)	2 (2.0)	0 (0.0)
Pulmonary	52 (51.0)	15 (14.7)	6 (5.9)	51 (50.0)	15 (14.7)	5 (4.9)
Dyspnea	43 (42.2)	10 (9.8)	3 (2.9)	32 (31.4)	12 (11.8)	4 (3.9)
Cough	15 (14.7)	0 (0.0)	0 (0.0)	19 (18.6)	0 (0.0)	0 (0.0)
Dermatology/Skin	48 (47.1)	5 (4.9)	1 (1.0)	35 (34.3)	2 (2.0)	0 (0.0)
Rash/desquamation	31 (30.4)	4 (3.9)	0 (0.0)	18 (17.6)	2 (2.0)	0 (0.0)
Dry skin	21 (20.6)	0 (0.0)	0 (0.0)	11 (10.8)	0 (0.0)	0 (0.0)
Hepatic	47 (46.1)	5 (4.9)	2 (2.0)	45 (44.1)	3 (2.9)	1 (1.0)
Alkaline phosphatase (increased)	27 (26.5)	0 (0.0)	0 (0.0)	29 (28.4)	1 (1.0)	0 (0.0)
SGOT (increased)	25 (24.5)	1 (1.0)	1 (1.0)	24 (23.5)	1 (1.0)	1 (1.0)
Bilirubin (increased)	14 (13.7)	1 (1.0)	1 (1.0)	10 (9.8)	1 (1.0)	1 (1.0)
Renal/Genitourinary	43 (42.2)	3 (2.9)	3 (2.9)	49 (48.0)	4 (3.9)	3 (2.9)
Creatinine	36 (35.3)	1 (1.0)	1 (1.0)	43 (42.2)	2 (2.0)	2 (2.0)
Musculoskeletal	42 (41.2)	8 (7.8)	2 (2.0)	41 (40.2)	11 (10.8)	3 (2.9)
Muscle weakness	41 (40.2)	6 (5.9)	1 (1.0)	38 (37.3)	10 (9.8)	3 (2.9)
Infection/Febrile Neutropenia	23 (22.5)	5 (4.9)	2 (2.0)	28 (27.5)	6 (5.9)	6 (5.9)
Infection without neutropenia	19 (17.6)	4 (3.9)	1 (1.0)	18 (17.6)	4 (3.9)	2 (2.0)

Incidence in ENL Controlled Clinical Trials

Table 7 lists treatment-emergent signs and symptoms that occurred in THALOMID® (thalidomide)-treated patients in controlled clinical trials in ENL. Doses ranged from 50 to 300 mg/day. All adverse events were mild to moderate in severity, and none resulted in discontinuation. Table 7also lists treatment-emergent adverse events that occurred in at least three of the THALOMID® (thalidomide)-treated HIV-seropositive patients who participated in an 8-week, placebo-controlled clinical trial. Events that were more frequent in the placebo-treated group are not included. (See **WARNINGS, PRECAUTIONS,** and **Drug Interactions**.)

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Table 7
Summary of Adverse Events (AEs)
Reported in Celgene-sponsored Controlled Clinical Trials

Body System/Adverse Event	All AEs Reported in ENL Patients 50 to 300 mg/day (N=24)	AEs Reported in ≥3 HIV-seropositive Patients Thalidomide 100 mg/day (N=36)	Thalidomide 200 mg/day (N=32)	Placebo (N=35)
Body as a Whole	**16 (66.7%)**	**18 (50.0%)**	**19 (59.4%)**	**13 (37.1%)**
Abdominal pain	1 (4.2%)	1 (2.8%)	1 (3.1%)	4 (11.4%)
Accidental injury	1 (4.2%)	2 (5.6%)	0	1 (2.9%)
Asthenia	2 (8.3%)	2 (5.6%)	7 (21.9%)	1 (2.9%)
Back pain	1 (4.2%)	2 (5.6%)	0	0
Chills	1 (4.2%)	0	3 (9.4%)	4 (11.4%)
Facial edema	1 (4.2%)	0	0	0
Fever	0	7 (19.4%)	7 (21.9%)	6 (17.1%)
Headache	3 (12.5%)	6 (16.7%)	6 (18.7%)	4 (11.4%)
Infection	0	3 (8.3%)	2 (6.3%)	1 (2.9%)
Malaise	2 (8.3%)	0	0	0
Neck pain	1 (4.2%)	0	0	0
Neck rigidity	1 (4.2%)	0	0	0
Pain	2 (8.3%)	0	1 (3.1%)	2 (5.7%)
Digestive System	**5 (20.8%)**	**16 (44.4%)**	**16 (50.0%)**	**15 (42.9%)**
Anorexia	0	1 (2.8%)	3 (9.4%)	2 (5.7%)
Constipation	1 (4.2%)	1 (2.8%)	3 (9.4%)	0
Diarrhea	1 (4.2%)	4 (11.1%)	6 (18.7%)	6 (17.1%)
Dry mouth	0	3 (8.3%)	3 (9.4%)	2 (5.7%)
Flatulence	0	3 (8.3%)	0	2 (5.7%)
Liver function tests multiple abnormalities	0	0	3 (9.4%)	0
Nausea	1 (4.2%)	0	4 (12.5%)	1 (2.9%)
Oral moniliasis	1 (4.2%)	4 (11.1%)	2 (6.3%)	0
Tooth pain	1 (4.2%)	0	0	0
Hemic and Lymphatic	**0**	**8 (22.2%)**	**13 (40.6%)**	**10 (28.6%)**
Anemia	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Leukopenia	0	6 (16.7%)	8 (25.0%)	3 (8.6%)
Lymphadenopathy	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Metabolic and Endocrine Disorders	**1 (4.2%)**	**8 (22.2%)**	**12 (37.5%)**	**8 (22.9%)**
Edema peripheral	1 (4.2%)	3 (8.3%)	1 (3.1%)	0
Hyperlipemia	0	2 (5.6%)	3 (9.4%)	1 (2.9%)
SGOT increased	0	1 (2.8%)	4 (12.5%)	2 (5.7%)
Nervous System	**13 (54.2%)**	**19 (52.8%)**	**18 (56.3%)**	**12 (34.3%)**
Agitation	0	0	3 (9.4%)	0
Dizziness	1 (4.2%)	7 (19.4%)	6 (18.7%)	0
Insomnia	0	0	3 (9.4%)	2 (5.7%)
Nervousness	0	1 (2.8%)	3 (9.4%)	0
Neuropathy	0	3 (8.3%)	0	0
Paresthesia	0	2 (5.6%)	5 (15.6%)	4 (11.4%)
Somnolence	9 (37.5%)	13 (36.1%)	12 (37.5%)	4 (11.4%)
Tremor	1 (4.2%)	0	0	0
Vertigo	2 (8.3%)	0	0	0
Respiratory System	**3 (12.5%)**	**9 (25.0%)**	**6 (18.7%)**	**9 (25.7%)**
Pharyngitis	1 (4.2%)	3 (8.3%)	2 (6.3%)	2 (5.7%)
Rhinitis	1 (4.2%)	0	0	4 (11.4%)
Sinusitis	1 (4.2%)	3 (8.3%)	1 (3.1%)	2 (5.7%)
Skin and Appendages	**10 (41.7%)**	**17 (47.2%)**	**18 (56.3%)**	**19 (54.3%)**
Acne	0	4 (11.1%)	1 (3.1%)	0
Dermatitis fungal	1 (4.2%)	2 (5.6%)	3 (9.4%)	0
Nail disorder	1 (4.2%)	0	1 (3.1%)	0
Pruritus	2 (8.3%)	1 (2.8%)	2 (6.3%)	2 (5.7%)
Rash	5 (20.8%)	9 (25.0%)	8 (25.0%)	11 (31.4%)
Rash maculo-papular	1 (4.2%)	6 (16.7%)	6 (18.7%)	2 (5.7%)
Sweating	0	0	4 (12.5%)	4 (11.4%)
Urogenital System	**2 (8.3%)**	**6 (16.7%)**	**2 (6.3%)**	**4 (11.4%)**
Albuminuria	0	3 (8.3%)	1 (3.1%)	2 (5.7%)
Hematuria	0	4 (11.1%)	0	1 (2.9%)
Impotence	2 (8.3%)	1 (2.8%)	0	0

Other Adverse Events Observed in ENL Patients

Thalidomide in doses up to 400 mg/day has been administered investigationally in the United States over a 19-year period in 1465 patients with ENL. The published literature describes the treatment of an additional 1678 patients. To provide a meaningful estimate of the proportion of the individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using a modified COSTART dictionary/terminology. These categories are used in the listing below. All reported events are included except those already listed in the previous table. Due to the fact that these data were collected from uncontrolled studies, the incidence rate cannot be determined. As mentioned previously, **no causal relationship between thalidomide and these events can be conclusively determined at this time**. These are reports of all adverse events noted by investigators in patients to whom they had administered thalidomide.

Body as a Whole: Abdomen enlarged, fever, photosensitivity, upper extremity pain.

***Cardiovascular System*:** Bradycardia, hypertension, hypotension, peripheral vascular disorder, tachycardia, vasodilation.

Digestive System: Anorexia, appetite increase/weight gain, dry mouth, dyspepsia, enlarged liver, eructation, flatulence, increased liver function tests, intestinal obstruction, vomiting.

Hemic and Lymphatic: ESR decrease, eosinophilia, granulocytopenia, hypochromic anemia, leukemia, leukocytosis, leukopenia, MCV elevated, RBC abnormal, spleen palpable, thrombocytopenia.

Metabolic and Endocrine: ADH inappropriate, amyloidosis, bilirubinemia, BUN increased, creatinine increased, cyanosis, diabetes, edema, electrolyte abnormalities, hyperglycemia, hyperkalemia, hyperuricemia, hypocalcemia, hypoproteinemia, LDH increased, phosphorus decreased, SGPT increased.

Muscular Skeletal: Arthritis, bone tenderness, hypertonia, joint disorder, leg cramps, myalgia, myasthenia, periosteal disorder.

Nervous System: Abnormal thinking, agitation, amnesia, anxiety, causalgia, circumoral paresthesia, confusion, depression, euphoria, hyperesthesia, insomnia, nervousness, neuralgia, neuritis, neuropathy, paresthesia, peripheral neuritis, psychosis.

Respiratory System: Cough, emphysema, epistaxis, pulmonary embolus, rales, upper respiratory infection, voice alteration.

Skin and Appendages: Acne, alopecia, dry skin, eczematous rash, exfoliative dermatitis, ichthyosis, perifollicular thickening, skin necrosis, seborrhea, sweating, urticaria, vesiculobullous rash.

Special Senses: Amblyopia, deafness, dry eye, eye pain, tinnitus.

Urogenital: Decreased creatinine clearance, hematuria, orchitis, proteinuria, pyuria, urinary frequency.

Other Adverse Events Observed in HIV-seropositive Patients

In addition to controlled clinical trials, THALOMID® (thalidomide) has been used in uncontrolled studies in 145 patients. Less frequent adverse events that have been reported in these HIV-seropositive patients treated with THALOMID® (thalidomide) were grouped into a smaller number of standardized categories using modified COSTART dictionary/terminology and these categories are used in the listing below. Adverse events that have already been included in the tables and narrative above, or that are too general to be informative are not listed.

Body as a Whole: Ascites, AIDS, allergic reaction, cellulitis, chest pain, chills and fever, cyst, decreased CD4 count, facial edema, flu syndrome, hernia, thyroid hormone level altered, moniliasis, photosensitivity reaction, sarcoma, sepsis, viral infection.

Cardiovascular System: Angina pectoris, arrhythmia, atrial fibrillation, bradycardia, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, heart arrest, heart failure, hypertension, hypotension, murmur, myocardial infarct, palpitation, pericarditis, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis.

Digestive System: Cholangitis, cholestatic jaundice, colitis, dyspepsia, dysphagia, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gum disorder, hepatitis, pancreatitis, parotid gland enlargement, periodontitis, stomatitis, tongue discoloration, tooth disorder.

Hemic and Lymphatic: Aplastic anemia, macrocytic anemia, megaloblastic anemia, microcytic anemia.

Metabolic and Endocrine: Avitaminosis, bilirubinemia, dehydration, hypercholesteremia, hypoglycemia, increased alkaline phosphatase, increased lipase, increased serum creatinine, peripheral edema.

Muscular Skeletal: Myalgia, myasthenia.

Nervous System: Abnormal gait, ataxia, decreased libido, decreased reflexes, dementia, dysesthesia, dyskinesia, emotional lability, hostility, hypalgesia, hyperkinesia, incoordination, meningitis, neurologic disorder, tremor, vertigo.

Respiratory System: Apnea, bronchitis, lung disorder, lung edema, pneumonia (including *Pneumocystis carinii* pneumonia), rhinitis.

Skin and Appendages: Angioedema, benign skin neoplasm, eczema, herpes simplex, incomplete Stevens-Johnson syndrome, nail disorder, pruritus, psoriasis, skin discoloration, skin disorder.

Special Senses: Conjunctivitis, eye disorder, lacrimation disorder, retinitis, taste perversion.

Other Adverse Events Observed in Post-Marketing Use

Cardiovascular System: Cardiac arrhythmias including atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome and EKG abnormalities.

Digestive System: Intestinal perforation.

Metabolic and Endocrine: Electrolyte imbalance including hypercalcemia or hypocalcemia, hyperkalemia and hypokalemia, hyponatremia, hypothyroidism, and increased alkaline phosphatase, tumor lysis syndrome.

Nervous System: Changes in mental status or mood including depression and suicide attempts, disturbances in consciousness including lethargy, syncope, loss of consciousness or stupor, seizures including grand mal convulsions and status epilepicus.

Skin and Appendages: Erythema multiforme.

Hemic and Lymphatic: Decreased white blood cell counts including neutropenia and febrile neutropenia, changes in prothrombin time.

Respiratory System: *Pleural effusion.*

Other Adverse Events in the Published Literature or Reported from Other Sources

The following additional events have been identified either in the published literature or from spontaneous reports from other sources: acute renal failure, amenorrhea, aphthous stomatitis, bile duct obstruction, carpal tunnel, chronic myelogenous leukemia, diplopia, dysesthesia, dyspnea, enuresis, erythema nodosum, erythroleukemia, foot drop, galactorrhea, gynecomastia, hangover effect, hypomagnesemia, hypothyroidism, lymphedema, lymphopenia, metrorrhagia, migraine, myxedema, nodular sclerosing Hodgkin's disease, nystagmus, oliguria, pancytopenia, petechiae, purpura, Raynaud's syndrome, stomach ulcer, and suicide attempt.

DRUG ABUSE AND DEPENDENCE

Physical and psychological dependence has not been reported in patients taking thalidomide. However, as with other tranquilizers/hypnotics, thalidomide too has been reported to create in patients habituation to its soporific effects.

OVERDOSAGE

There have been three cases of overdose reported, all attempted suicides. There have been no reported fatalities in doses of up to 14.4 grams, and all patients recovered without reported sequelae.

DOSAGE AND ADMINISTRATION

THALOMID® (thalidomide) MUST ONLY BE ADMINISTERED IN COMPLIANCE WITH ALL OF THE TERMS OUTLINED IN THE *S.T.E.P.S.*® PROGRAM. THALOMID® (thalidomide) MAY ONLY BE PRESCRIBED BY PRESCRIBERS REGISTERED WITH THE *S.T.E.P.S.*® PROGRAM AND MAY ONLY BE DISPENSED BY PHARMACISTS REGISTERED WITH THE *S.T.E.P.S.*® PROGRAM.

Drug prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing.

Multiple Myeloma

THALOMID® (thalidomide) is administered in combination with dexamethasone in 28-day treatment cycles. The dose of THALOMID® is 200 mg administered orally once daily with water, preferably at bedtime and at least 1-hour after the evening meal. The dose of dexamethasone is 40 mg daily administered orally on days 1-4, 9-12, and 17-20 every 28 days.

Patients who develop side effects such as constipation, oversedation, or peripheral neuropathy may benefit by either temporarily discontinuing the drug or continuing at a lower dose. With the abatement of these side effects, the drug may be started at a lower dose or at the previous dose based on clinical judgment.

Erythema Nodosum Leprosum

For an episode of cutaneous ENL, THALOMID® (thalidomide) dosing should be initiated at 100 to 300 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after the evening meal. Patients weighing less than 50 kilograms should be started at the low end of the dose range.

In patients with a severe cutaneous ENL reaction, or in those who have previously required higher doses to control the reaction, THALOMID® (thalidomide) dosing may be initiated at higher doses up to 400 mg/day once daily at bedtime or in divided doses with water, at least 1 hour after meals.

In patients with moderate to severe neuritis associated with a severe ENL reaction, corticosteroids may be started concomitantly with THALOMID® (thalidomide). Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

Dosing with THALOMID® (thalidomide) should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.

Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering, should be maintained on the minimum dose necessary to control the reaction. Tapering off medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.

HOW SUPPLIED

(THIS PRODUCT IS ONLY SUPPLIED TO PHARMACISTS REGISTERED WITH THE *S.T.E.P.S.*® PROGRAM - See BOXED WARNINGS.)

THALOMID® (thalidomide) Capsules is supplied in the following dosages:

50 mg capsules [white opaque], imprinted "Celgene / 50 mg" with a "Do Not Get Pregnant" logo.

Individual blister packs of 28 capsules (NDC 59572-205-14).

Boxes of 280 containing 10 prescription packs of 28 capsules each (NDC 59572-205-94).

100 mg capsules [tan], imprinted "Celgene / 100 mg" with a "Do Not Get Pregnant" logo.

Individual blister packs of 28 capsules (NDC 59572-210-15).

Boxes of 140 containing 5 prescription packs of 28 capsules each (NDC 59572-210-95).

200 mg capsules [blue], imprinted "Celgene / 200 mg" with a "Do Not Get Pregnant" logo.

Individual blister packs of 28 capsules (NDC 59572-220-16).

Boxes of 84 containing 3 prescription packs of 28 capsules each (NDC 59572-220-96).

STORAGE AND DISPENSING

PHARMACISTS NOTE:

BEFORE DISPENSING THALOMID® (thalidomide), YOU MUST ACTIVATE THE AUTHORIZATION NUMBER ON EVERY PRESCRIPTION BY CALLING THE CELGENE CUSTOMER CARE CENTER AT 1-888-4-CELGENE (1-888-423-5436) AND OBTAINING A CONFIRMATION NUMBER. YOU MUST ALSO WRITE THE CONFIRMATION NUMBER ON THE PRESCRIPTION. YOU SHOULD ACCEPT A PRESCRIPTION ONLY IF IT HAS BEEN ISSUED WITHIN THE PREVIOUS 7 DAYS (TELEPHONE PRESCRIPTIONS ARE NOT PERMITTED); DISPENSE NO MORE THAN A 4-WEEK (28-DAY) SUPPLY. A NEW PRESCRIPTION IS REQUIRED FOR FURTHER DISPENSING. DISPENSE BLISTER PACKS INTACT (CAPSULES CANNOT BE REPACKAGED); DISPENSE SUBSEQUENT PRESCRIPTIONS ONLY IF FEWER THAN 7 DAYS OF THERAPY REMAIN ON THE PREVIOUS PRESCRIPTION; AND EDUCATE ALL STAFF PHARMACISTS ABOUT THE DISPENSING PROCEDURE FOR THALOMID® (thalidomide).

This drug must not be repackaged.

Store at 25 ° C (77° F); excursions permitted to 15 – 30° C (59 -86° F). [See USP Controlled Room Temperature]. Protect from light.

Rx only and only able to be prescribed and dispensed under the terms of the *S.T.E.P.S.*® Restricted Distribution Program

Manufactured for Celgene Corporation

86 Morris Avenue

Summit, New Jersey 07901

1-(888) 423-5436

Important Information and Warnings for All Patients Taking THALOMID® (thalidomide)

WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS.

IF THALIDOMIDE IS TAKEN DURING PREGNANCY, IT CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY.

THALIDOMIDE SHOULD NEVER BE USED BY WOMEN WHO ARE PREGNANT OR WHO COULD BECOME PREGNANT WHILE TAKING THE DRUG. EVEN A SINGLE DOSE [1 CAPSULE (50 mg, 100 mg or 200 mg)] TAKEN BY A PREGNANT WOMAN CAN CAUSE SEVERE BIRTH DEFECTS

All Patients

- The patient understands that severe birth defects can occur with the use of THALOMID® (thalidomide).
- The patient has been warned by his/her doctor that an unborn baby will almost certainly have severe birth defects and can even die, if a woman is pregnant or becomes pregnant while taking THALOMID® (thalidomide).
- THALOMID® (thalidomide) will be prescribed ONLY for the patient and must NOT be shared with ANYONE, even someone who has similar symptoms.
- THALOMID® (thalidomide) must be kept out of the reach of children and should NEVER be given to women who are able to have children.
- The patient cannot donate blood while taking THALOMID® (thalidomide).
- The patient has read the THALOMID® (thalidomide) patient brochure and/or viewed the videotape, "Important Information for Men and Women Taking THALOMID® (thalidomide)" and understands the contents, including other possible health problems from THALOMID® (thalidomide), "side effects."
- The patient's doctor has answered any questions the patient has asked.
- The patient must participate in a telephone survey and patient registry, while taking THALOMID® (thalidomide).

Female Patients of Childbearing Potential

- The patient must not take THALOMID® (thalidomide) if she is pregnant, breast-feeding a baby, or able to get pregnant and not using the required two methods of birth control.
- The patient confirms that she is not now pregnant, nor will she try to become pregnant during THALOMID® (thalidomide) therapy and for at least 4 weeks after she has completely finished taking THALOMID® (thalidomide).
- If the patient is able to become pregnant, she must use at least one highly effective method and one additional effective method of birth control (contraception) AT THE SAME TIME:

At least one highly effective method	**AND**	**One additional effective method**
IUD		Latex condom
Hormonal (birth control pills, injections, or implants)		Diaphragm
Tubal ligation		Cervical cap
Partner's vasectomy		

- These birth control methods must be used for at least 4 weeks before beginning THALOMID® (thalidomide) therapy, during THALOMID® (thalidomide) therapy, and for 4 weeks following discontinuation of THALOMID® (thalidomide) therapy.
- The patient must use these birth control methods unless she completely abstains from heterosexual sexual contact.
- If a hormonal method (birth control pills, injections, or implants) or IUD is not medically possible for the patient, she may use another highly effective method or two barrier methods AT THE SAME TIME.
- The patient must have a pregnancy test done by her doctor within the 24 hours prior to starting THALOMID® (thalidomide) therapy, then every week during the first 4 weeks of THALOMID®(thalidomide) therapy.
- Thereafter, the patient must have a pregnancy test every 4 weeks if she has regular menstrual cycles, or every 2 weeks if her cycles are irregular while she is taking THALOMID® (thalidomide).
- The patient must immediately stop taking THALOMID® (thalidomide) and inform her doctor:

  If she becomes pregnant while taking the drug

  If she misses her menstrual period, or experiences unusual menstrual bleeding

  If she stops using birth control

  If she thinks FOR ANY REASON that she may be pregnant

  The patient understands that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception

Female Patients Not of Childbearing Potential

- The patient certifies that she is not now pregnant, nor of childbearing potential as she has been postmenopausal for at least 24 months (been through the change of life); or she has had a hysterectomy.
- The patient or guardian certifies that a prepubertal female child is not now pregnant, nor is of childbearing potential as menstruation has not yet begun, and/or the child will not be engaging in heterosexual sexual contact for at least 4 weeks before THALOMID® (thalidomide) therapy, during THALOMID® (thalidomide) therapy, and for at least 4 weeks after stopping therapy.

Male Patients

- The patient has been told by his doctor that he must NEVER have unprotected sexual contact with a woman who can become pregnant.
- Because THALOMID® (thalidomide) is present in semen, his doctor has explained that he must either completely abstain from sexual contact with women who are pregnant or able to become pregnant, or he must use a latex condom EVERY TIME

he engages in any sexual contact with women who are pregnant or may become pregnant while he is taking THALOMID® (thalidomide) and for 4 weeks after he stops taking the drug, even if he has had a successful vasectomy.

- The patient must inform his doctor:

  If he has had unprotected sexual contact with a woman who can become pregnant

  If he thinks FOR ANY REASON, that his sexual partner may be pregnant.

  The patient understands that if his doctor is not available, he can call 1-888-668-2528 for information on emergency contraception

- The patient cannot donate semen or sperm while taking THALOMID® (thalidomide).

Authorization:

This information has been read aloud to me in the language of my choice. I understand that if I do not follow all of my doctor's instructions, I will not be able to receive THALOMID® (thalidomide).

I now authorize my doctor to begin my treatment with THALOMID® (thalidomide).

Patient Signature_____Date_____

I have fully explained to the patient the nature, purpose, and risks of the treatment described above, especially the risks to women of childbearing potential. I have asked the patient if he/she has any questions regarding his/her treatment with THALOMID® (thalidomide) and have answered those questions to the best of my ability. I will comply with all of my obligations and responsibilities as a prescriber registered under the *S.T.E.P.S.*® restricted distribution program.

Prescriber Name (please type):_____

DEA Number:_____ Social Security Number if PA or NP: _____

Street Address: _____

City: _____ State: _____ Zip: _____

Prescriber Signature _____

REFERENCES

1. Manson JM. 1986. Teratogenicity. Cassarett and Doull's Toxicology: The Basic Science of Poisons. Third Edition. Pages 195-220. New York: MacMillan Publishing Co.
2. Smithels RW and Newman CG. 1992. J. Med. Genet. 29(10):716-723.
3. Sampaio EP, Kaplan G, Miranda A, *et al.* 1993. J. Infect. Dis. 168(2):408-414.
4. Sarno EN, Grau GE, Vieira LM, *et al.* 1991. Clin. Exp. Immunol. 84:103-108.
5. Sampaio EP, Moreira AL, Sarno EN, *et al.* 1992. J. Exp. Med. 175:1729-1737.

6. Nogueira AC, Neubert R, Helge H, *et al.* 1994. Life Sciences. 55(2):77-92.

7. Jacobson JM, Greenspan JS, Spritzler J, *et al.* 1997. New Eng. J. Med. 336(21):1487-1493

8. Eriksson T, Björkman S, Roth B, *et al.* 1998. Chirality. 10(3): 223-228.

9. Schumaker H, Smith RL, and Williams RT. 1965. Br. J. Pharmacol. 25:324-337.

10. Iyer CGS, Languillon J, Ramanujam K, et al. 1971. Bull. WHO. 45:719-732.

11. Sheskin J and Convit J. 1969. Intl. J. Leprosy. 37:135-146.

12. Waters MFR. 1971 Lepr. Rev. 42:26-42.

13. Unpublished data, on file at Celgene.

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