

15 July 1998

1 **WARNING: SEVERE, LIFE-THREATENING HUMAN BIRTH DEFECTS**

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

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

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

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

15 July 1998

23 **PRESCRIBERS**

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

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

34 Effective contraception (see **CONTRAINDICATIONS**) must be used for at least 1 month
35 before beginning thalidomide therapy, during thalidomide therapy, and for 1 month
36 following discontinuation of thalidomide therapy. Reliable contraception is indicated even
37 where there has been a history of infertility, unless due to hysterectomy or because the
38 patient has been post-menopausal for at least 24 months. Two reliable forms of
39 contraception must be used simultaneously unless continuous abstinence from reproductive
40 heterosexual sexual intercourse is the chosen method. Women of childbearing potential
41 should be referred to a qualified provider of contraceptive methods, if needed. Sexually
42 mature women who have not undergone a hysterectomy or who have not been
43 post-menopausal for at least 24 consecutive months (i.e., who have had menses at some
44 time in the preceding 24 consecutive months) are considered to be women of child-bearing
45 potential.

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

51 **Once treatment has started**, pregnancy testing should occur weekly during the first month
52 of use, then monthly thereafter in women with regular menstrual cycles. If menstrual cycles
53 are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and
54 counseling should be performed if a patient misses her period or if there is any abnormality
55 in menstrual bleeding.

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

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

15 July 1998

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 reproductive heterosexual intercourse is the chosen method. (Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal 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 child-bearing potential.).
- she acknowledges, in writing, her understanding of these warnings and of the need for using two reliable methods of contraception for one month prior to starting thalidomide therapy, during thalidomide therapy, and for one month after stopping 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.

15 July 1998

MALE PATIENTS

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

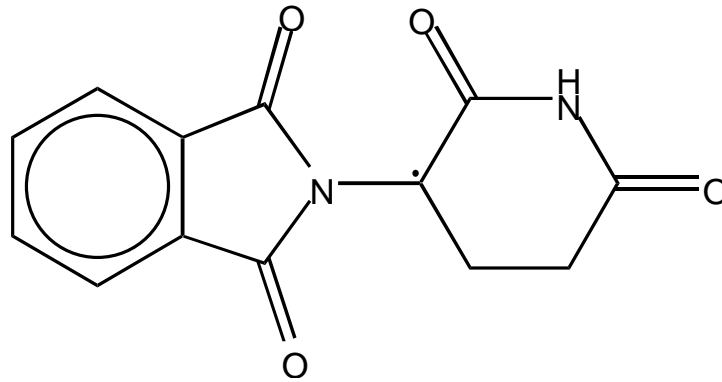
- he understands and can reliably carry out instructions.
- he is capable of complying with the mandatory contraceptive measures that are appropriate for men, patient registration, and patient survey as described in the *S.T.E.P.S.* program.
- he has received both oral and written warnings of the hazards 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 need to use barrier contraception when having sexual intercourse with women of childbearing potential, even if he has undergone successful vasectomy.
- he acknowledges, in writing, his understanding of these warnings and of the need for using barrier contraception (latex condom), even if he has undergone successful vasectomy, when having sexual intercourse with women of childbearing potential. Sexually mature women who have not undergone a hysterectomy or who have not been post-menopausal 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 child-bearing 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.

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

15 July 1998



Note: • = asymmetric carbon atom

115
116

117 Thalidomide is an off-white to white, nearly odorless, crystalline powder that is soluble at 25°C in
 118 dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a
 119 single asymmetric center and, therefore, may exist in either of two optically active forms
 120 designated S-(-) or R-(+). THALOMID (thalidomide) is an equal mixture of the S-(-) and R-(+)
 121 forms and, therefore, has a net optical rotation of zero.

122 THALOMID (thalidomide) is available in 50 mg capsules for oral administration. Active
 123 ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose,
 124 polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

125 CLINICAL PHARMACOLOGY

126 Mechanism of Action

127 Thalidomide is an immunomodulatory agent with a spectrum of activity that is not fully
 128 characterized. In patients with erythema nodosum leprosum (ENL) the mechanism of action is
 129 not fully understood.

130 Available data from *in vitro* studies and preliminary clinical trials suggest that the immunologic
 131 effects of this compound can vary substantially under different conditions, but, may be related to
 132 suppression of excessive tumor necrosis factor-alpha (TNF-α) production and down-modulation
 133 of selected cell surface adhesion molecules involved in leukocyte migration^{3,4,5,6}. For example,
 134 administration of thalidomide has been reported to decrease circulating levels of TNF-α in
 135 patients with ENL³, however, it has also been shown to increase plasma TNF-α levels in HIV-
 136 seropositive patients⁷.

137 Pharmacokinetics and Drug Metabolism

138 Absorption

139 The absolute bioavailability of thalidomide from THALOMID capsules has not yet been
 140 characterized in human subjects due to its poor aqueous solubility. In studies of both healthy
 141 volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations
 142 (T_{max}) of THALOMID ranged from 2.9 to 5.7 hours indicating that THALOMID is slowly
 143 absorbed from the gastrointestinal tract. While the extent of absorption (as measured by area

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.