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)] 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 AS NEGLIGIBLE AS POSSIBLE, THALOMID 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 1 month before beginning thalidomide therapy, during thalidomide therapy, and for 1 month 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 post-menopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from reproductive heterosexual sexual intercourse 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 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.

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 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.

Once treatment has started, pregnancy testing should occur weekly during the first month of use, then monthly thereafter 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 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.

MALE PATIENTS

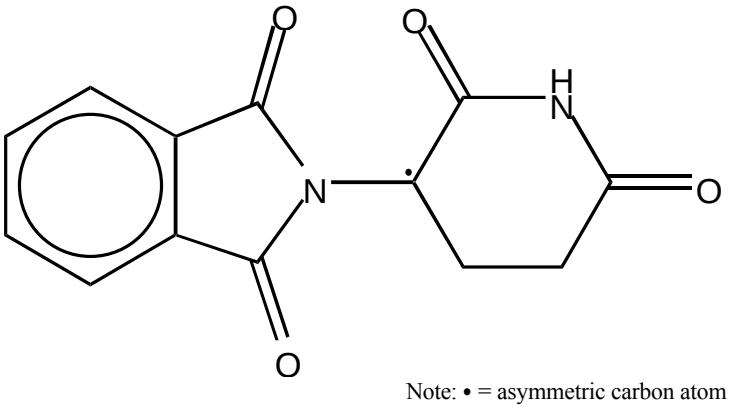
Thalidomide is contraindicated in sexually mature MALES unless the PATIENT MEETS ALL OF THE FOLLOWING CONDITIONS:

- 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



Note: • = asymmetric carbon atom

Thalidomide is an off-white to white, nearly 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 capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

Available data from *in vitro* studies and preliminary 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[3,4,5,6]. For example, administration of thalidomide has been reported to decrease circulating levels of TNF-α in patients with ENL[3], however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients[7].

Pharmacokinetics and Drug Metabolism

Absorption

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

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