

Thalidomide
PATIENT INFORMATION SHEET
Important Information and warnings for all the patients
'FOR THE USE OF HOSPITAL / INSTITUTE ONLY'

WARNING:
THALIDOMIDE SHOULD NEVER BE TAKEN BY PREGNANT WOMEN OR WOMEN CAPABLE OF BECOMING PREGNANT AS EVEN SINGLE DOSE CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY.

YOU SHOULD NOT TAKE THIS MEDICINE IF:

You have an allergic reaction to thalidomide.
You are pregnant or could become pregnant while taking the drug.
You are breast-feeding.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT TALIMYDE ?

Thalidomide is an immunomodulator. Thalidomide is used in multiple myeloma. Thalidomide is also used to treat and prevent the debilitating and disfiguring skin sores associated with erythema nodosum leprosum (ENL), an inflammatory complication of leprosy. Thalidomide can cause severe, life-threatening birth defects. If even one dose of thalidomide is taken, it can cause major birth defects including babies with no arms and legs; short arms and legs; missing bones; ear, eye, face, and heart abnormalities; and death of the baby. The greatest risk to the baby is during the first one to two months of pregnancy. Never use thalidomide if you could become pregnant, are already pregnant, or could make some one pregnant. Thalidomide may also be used for purposes other than those listed in this medication guide.

WHAT SHOULD I DISCUSS WITH PHYSICIAN BEFORE TAKING TALIMYDE ?

Before taking thalidomide tell your doctor, if you have,

1. Liver disease
2. Kidney disease
3. Heart disease/High blood pressure
4. HIV / AIDS
5. Blood or Bone marrow disease
6. Numbness, tingling, burning or pain in the hands or feet. Thalidomide may interact with other medications resulting in side effects or decrease in effects of one or both medication. So tell your physician about all medications you are taking.

HOW SHOULD I TAKE TALIMYDE ?

- Take TALIMYDE exactly as directed by your Physician.
- Take each dose with full glass of water.
- Take TALIMYDE at least after an hour of meal.
- Do not share this medication with any one else.

WHAT HAPPENS IF I MISS A DOSE ?

Take the missed dose as soon as you remember.
If it is almost time for the next dose, skip the dose you missed and take only the next regular scheduled dose.
Do not take two doses of thalidomide at a same time.

WHAT PRECAUTIONS SHOULD I TAKE BEFORE, DURING AND AFTER TALIMYDE TREATMENT ?

FOR FEMALES:

You must use at least two reliable methods of birth control for at least one month before starting the treatment, during the treatment and for one month after completion of treatment. Discuss with your physician about what kind of birth control to use.

Please perform pregnancy test every week for the first month of treatment then every month, if you have regular menstrual periods. If you miss menstrual period or if your menstrual bleeding is different than usual, immediately inform your doctor. You must stop taking thalidomide and inform your doctor if you suspect pregnancy while on therapy and pregnancy must be terminated.

You must not donate blood during treatment period.

FOR MALES :

You must use a latex condom while having sex during and after one month of treatment period.
You must inform your doctor if you have had unprotected sex with a woman or if your sexual partner become pregnant while you are on therapy.
You must not donate blood and semen while on thalidomide therapy.

WHAT SHOULD I AVOID DURING TALIMYDE TREATMENT ?

1. Avoid drinking alcohol.
2. This medication may cause drowsiness so you should avoid driving and operating machinery.
3. Avoid taking medication, which induce drowsiness such as tranquilizers, some cough preparations and sleeping pills

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Prescribing Information

For the use of a Registered Medical Practitioner or Hospital or Laboratory

Thalidomide Capsules USP 100 mg

TALIMYDE™



DESCRIPTION

Thalidomide, an immunomodulatory agent, is chemically (±)-alpha-(N-phthalimido) glutarimide. The empirical formula for thalidomide is C₁₇H₁₄N₂O₄ and the gram molecular weight is 258.2.

COMPOSITION

Talimide 100
Each hard gelatin capsule contains:
Thalidomide USP..... 100 mg

CLINICAL PHARMACOLOGY

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) production and down modulation of selected cell surface adhesion molecules involved in leukocyte migration¹⁻⁹. Its possible antitumor mechanism in multiple myeloma include a direct effect on multiple myeloma and/or bone marrow stromal cells, modulation of multiple myeloma stromal cell adhesion, suppression of multiple myeloma cell-sustaining cytokinins, antiangiogenic effects by repression vascular endothelial growth factor and basic fibroblast growth factor pathways, and immunomodulation such as induction of T_H1 T-cell response with secretion of interferon and interleukin-2. More recently, synergistic apoptotic signaling of thalidomide and dexamethasone has been observed⁸⁻¹⁰.

PHARMACOKINETICS

Absorption

The absolute bioavailability of thalidomide has not yet been characterized in human subjects due to its poor aqueous solubility. In studies, the mean time to peak plasma concentrations (T_{max}) of thalidomide ranged from 2.9 to 5.7 hours, indicating that 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. 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. Co-administration of 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

It is not known whether thalidomide is present in the ejaculate of males. The extent of plasma protein binding of thalidomide is unknown.

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 no-enzymatic hydrolysis in plasma to multiple metabolites. In a repeat dose study in which 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

The mean half-life of elimination ranges from approximately 5 to 7 hours following a single dose and is not altered upon multiple dosing. The precise metabolic fate and route of elimination of thalidomide in humans is not known. 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, only a very small amount 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 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 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 dysfunction have not been determined.

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 pharmacokinetic 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 Trials:
Two double blind randomized, controlled trials reported the dermatologic response to a seven day course of 100 mg thalidomide (four times daily) or control.

Double blind controlled clinical trials of thalidomide in patients with ENL: cutaneous response.

Reference	No. of Patients	No. Treatment courses	Percent Responding	
Lyer et al 11 Bull World Health Organization 1971;45:719	92	204	Thalidomide 75%	Aspirin 25%
Sheskin et al 12 Int J Lep 1969;37:135	52	173	Thalidomide 66%	Placebo 10%

Various studies indicate the potential of thalidomide in advance and relapsed multiple myeloma.

Barlgie et al. reported 48 % + 6% over all survival rate and 20% + 6% two year event free rate in 169 patients of advanced and/or refractory multiple myeloma treated with thalidomide (dose 200 - 800 mg)¹¹. Tosi et al., reported significant reduction in serum or urinary M protein ~ (monoclonal protein: an abnormal protein found in serum or urine of patient with multiple myeloma) in 46.6% of patients with advanced, relapsed or refractory multiple myeloma treated with 400 mg (median dose) / day of thalidomide⁹.

INDICATIONS

Thalidomide is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). It is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis, thalidomide is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

Thalidomide is also used in the treatment of multiple myeloma.

CONTRAINDICATIONS

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant. Thalidomide is contraindicated in patients who have demonstrated hypersensitivity to the drug and its components.

DOSE AND ADMINISTRATION

Drug prescribing to women of childbearing potential should be contingent upon initial and continued confirmed negative results of pregnancy testing. For an episode of cutaneous ENL, 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, 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. Steroid usage can be tapered and discontinued when the neuritis has ameliorated.

Dosing with 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.

For multiple myeloma:

For the treatment of multiple myeloma the dose range used is 200-800 mg daily.

WARNINGS

Birth Defects

If thalidomide is taken during pregnancy, it can cause severe birth defects or fetal death. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug. Even a single dose taken by a pregnant woman during her pregnancy can cause severe birth defects. Patients should be instructed to take thalidomide only as prescribed and not to share their thalidomide with anyone else. Because it is not known whether or not thalidomide is present in the ejaculate of males receiving the drug, males receiving thalidomide must always use a latex condom when engaging in sexual activity with women of childbearing potential.

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. Few reports of neuropathy have arisen in the treatment of ENL despite long-term thalidomide treatment. 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. 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/mm³. White blood cell count and differential should be monitored on an on-going basis, especially in patients who may be more prone to neutropenia, such as patients who are HIV-seropositive. If ANC decreases to below 750/mm³ 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 HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.

PRECAUTIONS

Hypersensitivity

Hypersensitivity to 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, thalidomide should be discontinued.

Bradycardia

Bradycardia in association with thalidomide use has been reported. At present there have been no reports of bradycardia requiring medical or other intervention. The clinical significance and underlying etiology of the bradycardia noted in some thalidomide-treated patients are unknown.

Pregnancy

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 reproductive heterosexual intercourse. If thalidomide is taken during pregnancy, it can cause severe birth defects or fetal death to an unborn baby. Thalidomide should never be used by women who are pregnant or who could become pregnant while taking the drug. If pregnancy does occur during treatment, the drug should be immediately discontinued.

Use in Nursing Home

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

No systematic studies in geriatric patients have been conducted. Thalidomide has been used in clinical trials in patients up to 90 years of age. Adverse events in patients over the age of 65 years did not appear to differ in kind from those reported for younger individuals.

DRUG INTERACTIONS

Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine. Peripheral Neuropathy: Medications known to be associated with peripheral neuropathy should be used with caution in patients receiving thalidomide.

Oral Contraceptives: No pharmacokinetic changes were observed when norethindrone and ethinyl estradiol coadministered with and without thalidomide 200 mg/day to steady-state levels.

Important No-Thalidomide Drug Interactions

Drugs That Interfere with Hormonal Contraceptives: Concomitant use of HIV-protease inhibitors, griseofulvin, rifampin, rifabutin, phenytoin, or carbamazepine with hormonal contraceptive agents, may reduce the effectiveness of the contraception. Therefore, women requiring treatment with one or more of these drug must use two other effective or highly effective methods of contraception or abstain from reproductive sexual intercourse.

ADVERSE EFFECTS

The most serious toxicity associated with thalidomide is its documented human teratogenicity. Thalidomide is associated with drowsiness/somnolence, peripheral neuropathy, dizziness/orthostatic hypotension, neutropenia, and HIV viral load increase. Hypersensitivity to thalidomide and bradycardia in patients treated with thalidomide have been reported. Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide.

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

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

Digestive System: Anorexia, appetite increase/weight gain, dry mouth, dyspepsia, enlarged liver, eruption, flatulence, increased liver function test, 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, alkaline phosphatase, amyloidosis, bilirubinemia, BUN increased, creatinine increase, 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, vasodilation.

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, seating urticaria, vesiculobullous rash.

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

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

OVERDOSAGE

Thalidomide is contraindicated in patients who have demonstrated hypersensitivity to the drug and its components.

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