

Front

To be sold by retail on the prescription of an Oncologist/Cancer Hospital/Institution only.

Rx

THALIVAX

Thalidomide Capsules USP

50mg,100mg & 200mg

WARNING: EMBRYO-FETAL TOXICITY AND VENOUS THROMBOEMBOLISM

Thalidomide should never be take by pregnant women or women capable of becoming pregnant as even a single dose can cause severe birth defects or death to an unborn baby.

VENOUS THROMBOEMBOLISM

The use of thalidomide in multiple myeloma results in an increased risk of venous thromboembolism, such as deep venous thrombosis and pulmonary embolism. This risk increases Significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone.

Composition

Each hard gelatin capsule contains:

Thalidomide USP.....50mg/100mg/200mg

Excipients.....q.s.

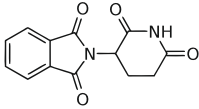
Color: Approved colors used in capsule shell.

DESCRIPTION

(Thalidomide) α-(N-phthalimido) gictarimide, is an imunomodulatory agent. Thalidomide is off-white to white, odorless, crystalline powder that is soluble at 25° 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-(+). Thalidomide is an equal mixture of the S-(-) and R-(+) forms and, therefore, has a set optical rotation of zero.

CHEMICAL STRUCTURE

The empirical formula for thalidomide is C₁₃H₁₀N₂O₃ and the gram molecular weight is 258.2
The structural formula for thalidomide is depicted below:



PHARMACOLOGY

Mechanism of action

The mechanism of action thalidomide is not completely understood. In vitro and in vivo studies indicate that it inhibits the production of tumor necrosis factor-alpha in monocytes. Thalidomide may induce the down regulation of integrin receptors and other surface adhesion proteins, reduce IgM production, alter CD4/CD8 T-cell ratios as well as increase the total numbers of CD8 and CD4 T-cells, and inhibit angiogenesis. Anti-inflammatory properties have been suggested through decreasing the production of oxygen-free radicals and other mediators in inflammatory response. Thalidomide may enhance cell-mediated immunity by directly stimulating cytotoxic T-cells

Pharmacokinetics

The mean time to take plasma concentrations range from 2.9 to 5.7 hours indicating that it is slowly absorbed from the gastrointestinal tract. Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple metabolites. The mean half life of elimination ranges from approximately 5 to 7 hours following a single dose and is not altered upon multiple dosing. Thalidomide has a renal clearance rate of 1.15 ml/min with less than 0.7 % of the dose excreted in the urine as unchanged drug.

INDICATIONS:

Thalidomide capsules is indicated for acute treatment of the cutaneous manifestations of moderate to severe Erythema Nodosum Laprosrum (ENL) and for the treatment of multiple myeloma.

CONTRAINDICATIONS:

Pregnancy

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant.

Hypersensitivity

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

ADVERSE EFFECTS:

The serious adverse reactions from thalidomide are

- Teratogenicity
- Venous Thromboembolism
- Drowsiness and Somnolence
- Peripheral Neuropathy
- Dizziness and Orthostatic Hypotension
- Increased HIV Viral Load
- Bradycardia
- Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
- Seizures and Tumor Lysis Syndrome
- Neutropenia
- Hypersensitivity

Teratogenicity

The most serious toxicity associated with thalidomide is its documented human teratogenicity. Thalidomide can cause severe birth defects in humans.

Venous thromboembolism

An increased risk of venous thromboembolism events (such as deep vein thrombosis and pulmonary embolism) has been reported in patients with multiple myeloma treated with thalidomide

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. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all.

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 ongoing basis especially in patients who may be more prone to neutropenia, such as patients who are HIV-seropositive.

Hypersensitivity

The occurrence of erythematous macular rash, possibly associated with fever, tachycardia, and hypotension, and if severe may necessitate interruption of therapy.

Dizziness and Orthostatic Hypotension

Patients should also be advised that thalidomide might cause dizziness and orthostatic hypotension. Thalidomide frequently causes drowsiness and somnolence.

In a clinical trial of thalidomide in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase.

Serious dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, which may be fatal have been reported.

Bradycardia, Seizures and Tumor Lysis Syndrome have been reponed.

The following additional adverse events have been identified during post approval use of thalidomide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: Cardiac arrhythmias including atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome, EKG abnormalities, myocardial infarction, intestinal perforation, gastrointestinal perforations, intestinal obstruction, electrolyte imbalance including hypercalcemia or hypocalcemia, hyperkalemia and hypokalemia, hyponatremia, hypothyroidism, increased alkaline phosphatase, tumor lysis syndrome, 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 epilepticus, Parkinson's disease, Erythema multiforme, toxic epidermal necrolysis, decreased white blood cell counts including neutropenia and febrile neutropenia, changes in prothrombin time, pancytopenia, pleural effusion, amenorrhea, sexual dysfunction, hypersensitivity, angioedema/urticaria, hearing impairment / deafness, renal failure.

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, suicide attempt, interstitial lung disease and severe infections (e.g., fatal sepsis including septic shock)

DRUG INTERACTIONS:

Thalidomide is not a substrate for cytochrome P450 (CYP450) isoenzymes and does not inhibit or induce human CYP450 enzymes in vitro. Therefore, pharmacokinetic drug-drug interactions are not anticipated when thalidomide is coadministered with drugs that are substrates, inhibitors or inducers of cytochrome P450. The use of opioids antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants concomitantly with thalidomide may cause an additive sedative effect and should be avoided.

Drugs which Cause Bradycardia

The use of drugs which slow cardiac conduction concomitantly with thalidomide may cause an additive bradycardic effect and should be used with caution. Cardiovascular medications which may cause bradycardia include calcium channel blockers, beta blockers, alpha/beta-adrenergic blockers, and digoxin. Non-cardiac drugs that may cause bradycardia include H₂blockers (e.g., famotidine, cimetidine), lithium, tricyclic antidepressants and neuromuscular blockers (succinylcholine).

Drugs which Cause Peripheral Neuropathy

The use of drugs which cause peripheral neuropathy (e.g., bortezomib, amiodarone, cisplatin, docetaxel, paclitaxel, vincristine, disulfiram, phenytoin, metronidazole, alcohol) can cause an additive effect and should be used with caution.

Hormonal Contraceptives

Hormonal contraceptives increase the risk of thromboembolism It is not known whether concomitant use of hormonal contraceptives further increases the risk of thromboembolism with thalidomide.

Warfarin

The single dose of warfarin had no effect on the pharmacokinetic profile of thalidomide.

Drugs that Interfere with Hormonal Contraceptives

Concomitant use of HIV-protease inhibitors, griseofulvin, modafinil, penicillins, rifampin, rifabutin, phenytoin, carbamazepine, or certain herbal supplements such as St. John's Wort with hormonal contraceptive agents may reduce the effectiveness of the contraception up to one month after discontinuation of these concomitant therapies. Therefore, women requiring treatment with one or more of these drugs must use two other effective or highly effective methods of contraception while taking thalidomide.

PRECAUTIONS AND WARNINGS:

Embryo-Fetal Toxicity

Thalidomide is a powerful human teratogen that induces a high frequency of severe and life-threatening birth defects, even after a single dose. Mortality at or shortly after birth has been reported in about 40% of infants. When there is no satisfactory alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Oral ingestion is the only type of maternal thalidomide exposure known to result in drug-associated birth defects. There are no specific data available regarding the reproductive risks of cutaneous absorption or inhalation of thalidomide however women of reproductive potential should avoid contact with thalidomide Capsules.

Females of Reproductive Potential

Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning thalidomide therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control beginning 4 weeks prior to initiating treatment with thalidomide, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of thalidomide therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing thalidomide therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles.

Males

Thalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking thalidomide and for up to 28 days after discontinuing thalidomide, even if they have undergone a successful vasectomy. Male patients taking thalidomide must not donate sperm.

Blood Donation

Patients must not donate blood during treatment with thalidomide and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to thalidomide.

Venous Thromboembolism

The use of 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. Consider thromboprophylaxis based on an assessment of individual patients' underlying risk factors. Patients and physicians should be observant for the signs and symptoms of thromboembolism. Patients should seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

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. Dose reductions may be required.

Peripheral 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 sit upright for a few minutes prior to standing up from a recumbent position.

Neutropenia

In neutropenia patients, if absolute neutrophil count 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. In HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter. Monitor patients for bradycardia and syncope. Dose reduction or discontinuation may be required. Medications known to decrease heart rate should be used with caution in patients receiving thalidomide. 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 thalidomide should not be resumed. 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. Monitor patients at risk of tumor lysis syndrome (e.g patients with high tumor burden prior to treatment) and take appropriate precautions. Some contraceptive methods may pose a higher risk of adverse effects or may be medically contraindicated in some patients treated with thalidomide. Because some patients may develop sudden, severe neutropenia and/or thrombocytopenia, use of an intrauterine device (IUD) or implantable contraception in these patients may carry an increased risk for infection or bleeding either at insertion, removal or during use. If the hypersensitivity reactions reappears when dosing is resumed, thalidomide should be discontinued.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Two-year carcinogenicity studies were conducted in male and female rats and mice. No compound-related tumorigenic effects were observed at the highest dose levels of 3,000 mg/kg/day to male and female mice

Thalidomide was neither mutagenic nor genotoxic in the following assays: the Ames bacterial (S. typhimurium and E. coli) reverse mutation assay, a Chinese hamster ovary cell (A852/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.

Pregnancy

Thalidomide can cause embryofetal harm when administered to a pregnant female and is contraindicated during pregnancy. Thalidomide is a human teratogen, inducing a high frequency of severe and life threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, 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 and mortality at or shortly after birth has been reported. Even a single dose taken by a pregnant woman can cause birth defects. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. 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.

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

In a study, patients ≥ 65 years of age had higher incidences of atrial fibrillation, constipation, fatigue, nausea, hypokalemia, deep venous thrombosis, hyperglycemia, pulmonary embolism, and asthenia compared to patients < 65.

Renal Impairment

No clinical studies were conducted with thalidomide in patients with mild, moderate or severe renal function.

Hepatic Impairment

No clinical studies have been conducted in patients with hepatic impairment.

DOSAGE AND ADMINISTRATION:

For multiple myeloma
The dose used in multiple myeloma is 200 mg daily.

For ENL

Thalidomide dosing should be started at 100 to 300 mg/day for cutaneous ENL. Dosing with thalidomide should continue until signs and symptoms of active reaction have subsided, usually for a period of 2 weeks

OVERDOSE:

Overdosages of up to 14.4 g have been reported in the literature. No fatalities have been reported and all overdosed patients recovered without sequelae There is no specific antidote for a thalidomide overdose

HANDLING AND DISPOSAL:

The potential hazards associated with cytotoxic agents are well established and proper precautions should be taken.

STORAGE:

Preserve in tight containers, protected from light. Store at 20°C- 25°C (68°F -77°F); excursions permitted to 15-30° C (59-86° F). [See USP Controlled Room Temperature]. Do not Repackaged.

SHELF LIFE: 24 Months

KEEP OUT OF REACH OF CHILDREN.

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