

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

THALOMID is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL). THALOMID is not indicated as monotherapy for such ENL treatment in the presence of moderate to severe neuritis

THALOMID is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence

Important Safety Information

WARNING: EMBRYO-FETAL TOXICITY AND VENOUS THROMBOEMBOLISM

EMBRYO-FETAL TOXICITY

If thalidomide is taken during pregnancy, it can cause severe birth defects or embryo-fetal death. Thalidomide should never be used by females who are pregnant or who could become pregnant while taking the drug. Even a single dose [1 capsule (regardless of strength)] 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 embryo-fetal exposure to THALOMID[®] (thalidomide) as negligible as possible, THALOMID[®] (thalidomide) is approved for marketing only through a special restricted distribution program: THALOMID REMS[®] program, approved by the Food and Drug Administration

You can get the information about THALOMID and the THALOMID REMS[®] program on the Internet at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436

VENOUS THROMBOEMBOLISM

The use of THALOMID (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. In one controlled trial, the rate of venous thromboembolism 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. Instruct patients to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Consider thromboprophylaxis based on an assessment of individual patients' underlying risk factors

CONTRAINDICATIONS

Pregnancy: See Boxed WARNINGS. THALOMID can cause fetal harm when administered to a pregnant female. THALOMID is contraindicated in females who are pregnant. Thalidomide is a powerful human teratogen, inducing 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. 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 risk to the fetus. If pregnancy occurs during thalidomide treatment, the drug should be discontinued immediately

Hypersensitivity: THALOMID is contraindicated in patients who have demonstrated hypersensitivity to the drug or its components

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: See Boxed WARNINGS

- **Females of Reproductive Potential:** Females of reproductive potential must avoid pregnancy for at least 4 weeks before beginning THALOMID 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 THALOMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of THALOMID therapy
- **Males:** Thalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking THALOMID and for up to 4 weeks after discontinuing THALOMID, even if they have undergone a successful vasectomy. Male patients taking THALOMID must not donate sperm
- **Blood Donation:** Patients must not donate blood during treatment with THALOMID and for 4 weeks following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to THALOMID

THALOMID REMS[®] program: See Boxed WARNINGS:

Because of the embryo-fetal risk, THALOMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the THALOMID REMS[®] program. Prescribers and pharmacies must be certified with the program; and patients must sign an agreement form and comply with the requirements. Further information about the THALOMID REMS[®] program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436

Venous and Arterial Thromboembolism: The use of THALOMID in patients with MM results in an increased risk of venous thromboembolism, such as deep venous thrombosis and pulmonary embolism. This risk increases significantly when THALOMID is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolism was 22.5% in patients receiving THALOMID in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone ($p = 0.002$). Ischemic heart disease (11.1%), including myocardial infarction (1.3%), and stroke (cerebrovascular accident, 2.6%) have also occurred in patients with previously untreated MM treated with THALOMID and dexamethasone compared to placebo and dexamethasone (4.7%, 1.7%, and 0.9%, respectively) in one clinical trial. Consider thromboprophylaxis based on an assessment of individual patients' underlying risk factors. Advise patients to seek immediate medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Agents that may increase the risk of thromboembolism should be used with caution in patients receiving THALOMID

Drowsiness and Somnolence: THALOMID 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. Dose reductions may be required

Peripheral Neuropathy: THALOMID is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, $\geq 10\%$, potentially severe adverse reaction of treatment with THALOMID that may be irreversible

Dizziness and Orthostatic Hypotension: Patients should be advised that THALOMID 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 clinical use of THALOMID. Treatment should not be initiated with an absolute neutrophil count (ANC) of $< 750/\text{mm}^3$. 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 $750/\text{mm}^3$ while on treatment, the patient's medication regimen should be re-evaluated and, if the neutropenia persists, consideration should be given to withholding THALOMID if clinically appropriate

Thrombocytopenia: Thrombocytopenia including Grade 3 or 4 occurrences has been reported with the use of THALOMID. Monitor blood counts including platelets. Dose reduction, delay or discontinuation may be required. Monitor for signs and symptoms of bleeding including petechiae, epistaxis, and gastrointestinal bleeding, especially if concomitant medication may increase risk of bleeding

Increased HIV Viral Load: In a randomized, placebo controlled trial of THALOMID in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase (median change = 0.42 log₁₀ copies HIV RNA/mL, p=0.04 compared to placebo). A similar trend was observed in a second, unpublished study conducted in patients who were HIV-seropositive. The clinical significance of this increase is unknown

Bradycardia: Bradycardia in association with THALOMID use has been reported. 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

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 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 should not be resumed

Seizures: Although not reported from pre-marketing clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of THALOMID in clinical practice. Patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely

Tumor Lysis Syndrome: Monitor patients at risk of tumor lysis syndrome (e.g., patients with high tumor burden prior to treatment) and take appropriate precautions

Contraceptive Risks: Some contraceptive methods may pose a higher risk of adverse effects or may be medically contraindicated in some patients treated with THALOMID. 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. Treatment with THALOMID, the presence of an underlying malignancy, and/or use of an estrogen-containing contraceptive can each increase the risk of thromboembolism. It is not known if these risks of thromboembolism are additive. However, they should be taken into consideration when choosing contraceptive methods

Hypersensitivity: Hypersensitivity to THALOMID 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 should be discontinued

ADVERSE REACTIONS:

Multiple Myeloma

- The safety analysis in Study 1 was conducted on 204 patients who received treatment. The most frequently reported adverse reactions (all grades) in multiple myeloma patients (occurring in ≥20% of patients treated with THALOMID /dexamethasone compared with dexamethasone alone) in Study 1 were: fatigue (79% vs 71%), hypocalcemia (72% vs 59%), edema (56% vs 46%), constipation (55% vs 28%), neuropathy-sensory (54% vs 28%), dyspnea (42% vs 31%), muscle weakness (40% vs 37%), leukocytes (decreased) (35% vs 29%), neutrophils (decreased) (31% vs 24%), rash/desquamation (30% vs 18%), confusion (28% vs 12%), anorexia (28% vs 24%), nausea (28% vs 22%), anxiety/agitation (26% vs 14%), tremor (26% vs 6%), fever (24% vs 20%), thrombosis/embolism (22% vs 5%), weight loss (23% vs 21%), neuropathy-motor (22% vs 16%), weight gain (22% vs 13%), dry skin (21% vs 11%), and dizziness/lightheadedness (20% vs 14%)
- The most frequently reported Grade 3/4 adverse drug reactions occurring in ≥ 10% of patients treated with THALOMID /dexamethasone compared with dexamethasone alone) in Study 1 were: fatigue (17% vs

13%), hypocalcemia (11% vs 5%), dyspnea (13% vs 15%), neutrophils (decreased) (10% vs 10%), thrombosis/embolism (21% vs 5%)

- Twenty-three percent of patients (47/204) discontinued due to adverse reactions; 30% (31/102) from the THALOMID/dexamethasone arm and 16% (16/102) from the dexamethasone alone arm
- The safety analysis in Study 2 was conducted on 466 patients who received treatment. The most common adverse drug reactions (all grades) reported in ($\geq 20\%$) patients treated with THALOMID/dexamethasone were constipation (50% vs 21%), peripheral edema (34% vs 25%), tremor (26% vs 12%), asthenia (24% vs 20%), dizziness (23% vs 14%) and fatigue (21% vs 16%)
- The most frequently reported Grade 3/4 adverse drug reactions occurring in $> 5\%$ of patients treated with THALOMID /dexamethasone compared with dexamethasone alone) in Study 2 were: deep vein thrombosis (12% vs 2%), pulmonary embolism (7% vs 2%), pneumonia NOS (7% vs 6%), asthenia (5% vs 2%) and atrial fibrillation (5% vs 3%)
- Twenty-six percent of patients (121/466) discontinued due to adverse events; 37% (86/234) from the THALOMID/dexamethasone arm and 15% (35/232) from the placebo/dexamethasone arm

Erythema Nodosum Leprosum

- Common adverse events, greater than or equal to 8%, reported in THALOMID treated patients in controlled clinical trials in ENL: somnolence (38%), rash (21%), headache (13%), asthenia (8%), malaise (8%), pain (8%), vertigo (8%), pruritus (8%), and impotence (8%)

DRUG INTERACTIONS

Thalidomide is not a substrate of the cytochrome P450 system. At therapeutic concentrations, THALOMID is not an inhibitor or inducer of human cytochrome P450 enzymes in vitro. Pharmacokinetic drug-drug interactions with substrates, inhibitors or inducers of CYP450 are not anticipated.

The use of opioids, antihistamines, antipsychotics, anti-anxiety agents, or other CNS depressants concomitantly with THALOMID may cause an additive sedative effect and should be avoided

Drugs which cause bradycardia or peripheral neuropathy may cause additive effects and should be used with caution

Hormonal contraceptives increase the risk of thromboembolism

In 13 healthy men, the pharmacokinetic profile and international normalized ratio (INR) of prothrombin time for warfarin, following a single oral dose of 25 mg, were similar with and without the coadministration of THALOMID 200 mg/day at steady-state levels. The single dose of warfarin had no effect on the pharmacokinetic profile of THALOMID

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

Erythropoietic agents, or other agents that may increase the risk of thromboembolism, such as estrogen containing therapies, should be used with caution in MM patients receiving THALOMID with dexamethasone

Use in Specific Populations

Pregnancy: See Boxed WARNINGS. If pregnancy does occur during treatment, immediately discontinue the drug and refer the patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to THALOMID to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436. There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to THALOMID during pregnancy as well as female partners of male patients who are exposed to THALOMID. This registry is also used to understand the root cause for the pregnancy

Lactation: There is no information regarding the presence of thalidomide in human milk, the effects of THALOMID on the breastfed infant, or the effects of THALOMID on milk production. Thalidomide is excreted in the milk of lactating rabbits. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from THALOMID, advise female patients not to breastfeed during treatment with THALOMID

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

Renal and Hepatic Impairment: No clinical studies were conducted with THALOMID in patients with mild, moderate, or severe renal function or with hepatic impairment

Please see [accompanying or enclosed, etc] full Prescribing Information, including Boxed WARNINGS.