720 mm

DOMIDE Capsules 50 mg (Thalidomide)

【WARNING】

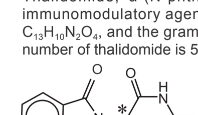
SEVERE, LIFE-THREATENING HUMAN BIRTH DEFFECTS.

If thalidomide is taken during pregnancy, it can cause severe birth defects or death to an unborn baby. Thalidomide should never be used in 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. Before starting treatment, patients have to read and sign the informed consent form for female/male patients for taking DOMIDE and must comply with the instructions and follow physicians' directions. Once treatment has started, if you are unable or unwilling to comply with the instructions or directions, you have to stop taking DOMIDE and inform your doctors.

【DESCRIPTION】

Each DOMIDE capsule contains 50mg of active ingredient, thalidomide. The appearance of capsules is hard capsules, and white body orange cap, imprinted with "THADO" in black print on both of the cap and the body.

Thalidomide, α-(N-phthalimido) glutarimide, is an immunomodulatory agent. The empirical formula 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.



Note: * = asymmetric carbon

Thalidomide is an off-white to white, 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-(+). DOMIDE (thalidomide) is an equal mixture of the S-(-) and R-(+) forms and, therefore, has a net optical rotation of zero.

Thalidomide is available in 50 mg capsules for oral administration.

【Excipients】

Avicel ph-l02; Lactose Monohydrate; Lactose spray-dried; Corn starch; Silicon dioxide; Stearic acid; Magnesium stearate.

【CLINICAL PHARMACOLOGY】

Mechanism of Action

The mechanism of action of thalidomide is not fully understood. Thalidomide possesses immunomodulatory, anti-inflammatory and antiangiogenic properties. Available data from in vitro studies and 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. For example, administration of thalidomide has been reported to decrease circulating levels of TNF-α in patients with erythema nodosum leprosum (ENL), however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients. Other anti-inflammatory and immunomodulatory properties of thalidomide may include suppression of macrophage involvement in prostaglandin synthesis, and modulation of interleukin-10 and interleukin-12 production by peripheral blood mononuclear cells. Thalidomide treatment of multiple myeloma patients is accompanied by an increase in the number of circulating natural killer cells, and an increase in plasma levels of interleukin-2 and interferon-gamma (T cell-derived cytokines associated with cytotoxic activity). Thalidomide was found to inhibit angiogenesis in a human umbilical artery explant model *in vitro*. The cellular processes of angiogenesis inhibited by thalidomide may include the proliferation of endothelial cells.

【Pharmacokinetics and Drug Metabolism】

Absorption：

The absolute bioavailability of thalidomide capsules has not yet been obtained in human subjects due to its poor aqueous solubility. However, the capsules are 90% bioavailable relative to an oral PEG solution.

In studies of both healthy volunteers and subjects with Hansen's disease, the mean time to peak plasma concentrations (T_{max}) is 2.9 to 5.7 hours indicating that thalidomide is slowly absorbed from 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 (see Table 1 below). Coadministration 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.

Table 1: Pharmacokinetic Parameter Values for Thalidomide Mean (%CV)]

Population /Single Dose	AUC (µg-hr/mL)	C_{max} (µg/mL)	T_{max} (hrs)	Half-life (hrs)
Healthy Subjects (n=14)				
50 mg	4.9 (16%)	0.62 (52%)	2.9 (66%)	5.52 (37%)
200 mg	18.9 (17%)	1.76 (30%)	3.5 (57%)	5.53 (25%)
400 mg	36.4 (26%)	2.82 (28%)	4.3 (37%)	7.29 (36%)
Patients with Hansen's Disease (n=6)				
400 mg	46.4 (44.1%)	3.44 (52.6%)	5.7 (27%)	6.86 (17%)

Distribution

In human blood plasma, the geometric mean plasma protein binding was 55% and 66%, respectively, for (+)-(R)- and (-)-(S)-thalidomide. In a pharmacokinetic study of thalidomide in HIV-seropositive adult male subjects receiving thalidomide 100 mg/day, thalidomide was detectable in the semen.

Metabolism：

At the present time, the exact metabolic route of thalidomide is not known in humans. Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple products. In a repeat dose study in which thalidomide 200 mg was administered to 10 healthy females for 18 days, 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：

As indicated in Table 1(above), the mean half-life of elimination ranges from approximately 5 to 7 hours following a single dose and is not altered upon multiple dosing. As noted in the metabolism subsection, the precise metabolic fate and route of thalidomide is in humans is not know at this time. 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 hours after dosing. Although thalidomide is thought to be hydrolyzed to a number of metabolites, only a very small amount (0.02% of the administered dose) 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.

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 (AUC) and in increased peak plasma levels (C_{max}) (see Table 1). The clinical significance of this increase is unknown.

Patients with Renal Insufficiencye: The pharmacokinetics of thalidomide in patients with renal impairment have not been determined. In a study of 6 patients with end-stage renal disease, thalidomide (200 mg/day) was administered on a non-dialysis day and on a dialysis day. Comparison of concentration-time profiles on a non-dialysis day and during dialysis where blood samples were collected at least 10 hours following the dose, showed that the mean total clearance increased by a factor of 2.5 during hemodialysis.

Because the dialysis was performed 10 hours following administration of the dose, the drug-concentration time curves were not statistically significantly different for days patients were on and off of dialysis. Thus, no dosage adjustment is needed for renally-impaired patients on dialysis.

Patients with Hepatic Disease: The pharmacokinetics of thalidomide in patient 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 pharmacokinetics has not been conducted, 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 STUDIES】

In Newly Diagnosed Multiple Myeloma

The efficacy of thalidomide in multiple myeloma was demonstrated in a randomized, multi-center open-label study of 207 newly diagnosed patients. This study randomized symptomatic patients with newly diagnosed multiple myeloma to thalidomide plus dexamethasone (Thal + Dex; N = 103) versus dexamethasone alone (Dex alone; N=104). The thalidomide dose was 200 mg daily and the dexamethasone dose was 40 mg orally once daily on days 1-4, 9-12, and 17-20 every 28-days. Each group was treated for four 28-day cycles.

Baseline demographic and disease characteristics for the study population are summarized in Tables 2 and 3 respectively. Response rate was the primary endpoint. Response rates based on serum or urine M-protein measurements were significantly higher in the combination arm (51.5% compared with 35.6% for dexamethasone alone).

Table 2: Baseline Patient Demographics

Characteristic	Thal + Dex (N = 103)	Dex alone (N=104)
Age (years)		
Median	65	68
Range	37-83	38-83
Gender[1]		
Male	53 (51%)	61 (59%)
Female	50 (49%)	42 (40%)
Race[2]		
Caucasian	90 (87%)	90 (87%)
Black	11 (11%)	11 (11%)
Other	1 (1%)	2 (2%)

1. Missing information for 1 patient in the Dex alone group
2. Missing information for 1 patient per arm

Table 3: Baseline Disease Characteristics

Characteristic	Thal + Dex (N = 103)	Dex alone (N=104)
Stage (Durie-Salmon), N(%)[1]		
I	14 (13.6%)	17 (16.3%)
II	47 (45.6%)	44 (42.3%)
III	41 (39.8%)	43 (41.3%)
Immunoglobulin Type, N(%)[2]		
IgA	21 (20.4%)	22 (21.2%)
IgG	63 (61.2%)	60 (57.7%)
IgM	0 (0.0%)	1 (1.0%)
Biclonal	0 (0.0%)	1 (1.0%)
Lytic Lesion[3]		
None	28 (27.1%)	14 (13.5%)
1-3 lesions	24 (23.3%)	19 (18.3%)
> 3 lesions	34 (33.0%)	41 (39.4%)
Serum Light Chain[4]		
Kappa	59 (57.3%)	53 (51.0%)
Lamba	28 (27.2%)	40 (38.5%)

1. Missing information for 1 patient in Thal + Dex arm
2. Missing information for 19 patients in Thal + Dex arm and 20 patients in Dex alone arm
3. Missing information for 17 patients in Thal + Dex arm and 30 patients in Dex alone arm
4. Missing information for 16 patients in Thal + Dex arm and 11 patients in Dex alone arm

Erythema Nodosum Leprosum (ENL)

The primary data demonstrating the efficacy of thalidomide in the treatment of the cutaneous manifestations of moderate to severe ENL are derived from the published medical literature and from a retrospective study of 102 patients treated by the U.S. Public Health Service.

Two double-blind, randomized, controlled trials reported the dermatologic response to a 7-day course of 100 mg thalidomide (four times daily) or control. Dosage was lower for patients under 50 kg in weight

Table 4: Double-Blind, Controlled Clinical Trials of Thalidomide in Patients with ENL: Cutaneous response

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

*In patients with cutaneous lesions

** Iyer: Complete response or lesions absent

** Sheskin: Complete improvement + "striking" improvement (i.e.,> 50% improvement)

Waters reported the results of two studies, both double-blind, randomized, placebo controlled, crossover trials in a total of 10 hospitalized, steroid-dependent patients with chronic ENL treated with 100 mg thalidomide or placebo (three times daily). All patients also received dapsone. The primary endpoint was reduction in weekly steroid dosage.

Table 5: Double-Blind, Controlled Trial of Thalidomide in Patients with ENL: Reduction in Steroid Dosage

Reference	Duration of Treatment	No. of Patients	Number Responding	
			Thalidomide	Placebo
Waters	4 weeks	9	4/5	0/4
Lep Rev 1971; 42: 26	6 weeks (crossover)	8	8/8	1/8

Data on the efficacy of thalidomide in prevention of ENL relapse were derived from a retrospective evaluation of 102 patients treated under the auspices of the U.S. Public Health Service. A subset of patients with ENL controlled on thalidomide demonstrated repeated relapse upon drug withdrawal and remission with reinstitution of therapy.

Twenty U.S. patients between the ages of 11 and 17 years were treated with thalidomide, generally at 100 mg daily. Response rates and safety profiles were similar to that observed in the adult population.

Thirty-two other published studies containing over 1600 patients consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL with thalidomide.

【Indication】

Multiple Myeloma :

-DOMIDE in combination with melphalan and prednisone is indicated for the treatment of patients with untreated multiple myeloma ≧ 65 years or ineligible for high dose chemotherapy.

-DOMIDE in combination with dexamethasone is indicated for induction therapy prior to high dose chemotherapy with autologous stem cell rescue, for the treatment of patients with untreated multiple myeloma.

-The effectiveness of thalidomide when used in combination with dexamethasone is based on response rates. There are no controlled trials demonstrating an improvement in survival.

Erythema Nodosum Leprosum (ENL) :

DOMIDE is indicated for the acute treatment of the cutaneous manifestations of moderate to severe ENL.

DOMIDE is not indicated as monotherapy for such as ENL treatment in the presence of moderate to severe neuritis.

DOMIDE is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestation of ENL recurrence.

【CONTRAINDICATIONS】

Pregnancy: Category X

Due to its known human teratogenicity, even following a single dose, thalidomide is contraindicated in pregnant women and women capable of becoming pregnant. (See BOXED WARNINGS.) When there is no alternative treatment, women of childbearing potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy. Women must commit either to abstain continuously from heterosexual sexual contact or to use two methods of reliable birth control, including at least one highly effective method (e.g., IUD, hormonal contraception, tubal ligation, or partner's vasectomy) and one additional effective method (e.g., latex condom, diaphragm, or cervical cap), beginning 4 weeks prior to initiating treatment with thalidomide, during therapy with thalidomide, and continuing for 4 weeks following discontinuation of thalidomide therapy. If hormonal or IUD contraception is medically contraindicated (see PRECAUTIONS: Drug Interactions), two other effective or highly effective methods may be used.

Women of childbearing potential being treated with thalidomide should have a pregnancy test (sensitivity of at least 50 mIU/mL), and a prescription must not be issued until a written report of a negative pregnancy test has been obtained by the prescriber. The test should be performed within the 24 hours prior to beginning thalidomide therapy and then weekly during the first 4 weeks of thalidomide therapy, then at 4 week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy occurs during thalidomide treatment, thalidomide must be discontinued immediately. Under these conditions, the patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

Thalidomide is contraindicated in patients who have demonstrated hypersensitivity to the drug or other components.

【WARNINGS】

Birth Defects:

Thalidomide can cause severe birth defects in humans. (See BOXED WARNINGS and CONTRAINDICATIONS.) Patients should be instructed to take thalidomide only as prescribed and not to share their thalidomide with anyone else. Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

Thrombotic Events:

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. In one controlled trial, the rate of venous thromboembolic events 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. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Preliminary data suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

Arterial Thromboembolic Events:

Cases of arterial thromboembolic events (ATEE), including fatal cass, have been reported in patients treated with thalidomide. These events included principally myocardial infarction, cerebrovascular accident, transient ischaemic attack and other arterial thromboembolic events. The risk appears to be greatest during the first 5 months of therapy. Risk factors associated with ATEE, in addition to the underlying malignant disease, age ≥ 65 years, and being male, included hyperlipidemia, hypertension, diabetes, obesity, renal disease, and tobacco use.

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.

Pulmonary Hypertension:

Cases of pulmonary hypertension, some fatal, have been reported in patients treated with thalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during thalidomide therapy.

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. The correlation with cumulative dose is unclear. Symptoms may occur some time after thalidomide treatment has been stopped and may resolve slowly or not at all.

Few reports of neuropathy have arisen in the treatment of ENL despite long-term thalidomide treatment. However, the inability clinically to differentiate thalidomide neuropathy from the neuropathy often seen in Hansen's disease makes it difficult to determine accurately the incidence of thalidomide-related neuropathy in ENL patients treated with thalidomide.

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. Patients should be regularly counseled, questioned, and evaluated for signs or symptoms of peripheral neuropathy. 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 limited 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/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/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 thalidomide if clinically appropriate.

Infections:

Cases of viral reactivation have been reported in patients receiving thalidomide, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation.

Some of the cases of herpes zoster reactivation resulted in disseminated herpes zoster, requiring a temporary hold of the treatment with thalidomide and adequate antiviral treatment.

Some of the cases of HBV reactivation progressed to acute hepatic failure and resulted in discontinuation of thalidomide. Hepatitis B virus status should be established before initiating treatment with thalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

Previously infected patients should be closely monitored for signs and symptoms of viral reactivation, including active HBV infection, throughout therapy.

Increased HIV Viral Load:

In a randomized, placebo controlled trial of thalidomide in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase (median change = 0.42 log_{10} 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. Both studies were conducted prior to availability of highly active antiretroviral therapy. Until the clinical significance of this finding is further understood, in HIV-seropositive patients, viral load should be measured after the first and third months of treatment and every 3 months thereafter.

【PRECAUTIONS】

General:

The only type of thalidomide exposure known to result in drug associated birth defects are as a result of direct oral ingestion of thalidomide. Currently no specific data are available regarding the cutaneous absorption or inhalation of thalidomide in women of childbearing potential and whether these exposures may result in any birth defects. Patients should be instructed to not extensively handle or open thalidomide capsules and to maintain storage of capsules in blister packs until ingestion. If there is contact with non-intact thalidomide capsules or the powder contents, the exposed area should be washed with soap and water.

Thalidomide has been shown to be present in the serum and semen of patients receiving thalidomide. If healthcare providers or other care givers are exposed to body fluids from patients receiving thalidomide, appropriate precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to thalidomide or the exposed area should be washed with soap and water.

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, Cases of bradycardia have been reported, some required medical interventions. The clinical significance and underlying etiology of the bradycardia noted in some thalidomide-treated patients are presently unknown.

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. 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.

Seizures:

Although not reported from pre-marketing controlled clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of thalidomide in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence. 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.

Second Primary Malignancies- Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS):

AML and MDS have been observed in an ongoing clinical trial in patients with previously untreated MM receiving the combination melphalan, prednisone, and thalidomide (MPT). AML and MDS have been rarely reported in the post-market setting.

The risk of AML and MDS must be taken into account before initiating treatment with thalidomide in combination with melphalan and prednisone (MPT). Physician should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

Information for Patients (See BOXED WARNINGS)

Patients should be instructed about the potential teratogenicity of thalidomide and the precautions that must be taken to preclude fetal exposure as per the informed consent and boxed warnings in this package insert. Patients should be instructed to take thalidomide only as prescribed in compliance with all of the provisions of the informed consent.

Patients should be instructed to not extensively handle or open thalidomide capsules and to maintain storage of capsules in blister packs until ingestion.

Patients should be instructed not to share medication with anyone else.

Patients should be instructed that 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 machinery. Patients should be instructed that thalidomide may potentiate the somnolence caused by alcohol.

Patients should be instructed that thalidomide can cause peripheral neuropathies that may be initially signaled by numbness, tingling, or pain or a burning sensation in the feet or hands. And patients should report such occurrences to their prescriber immediately.

Patients should also be instructed 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.

Patients should be instructed that they are not permitted to donate blood while taking thalidomide. In addition, male patients are not permitted absolutely to donate sperm while taking thalidomide.

Patients should be educated about the signs and symptoms of thromboembolism and instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling.

Lactose Intolerance:

The capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Laboratory Tests

Pregnancy Testing: (See WARNINGS)

Women of childbearing potential should have a pregnancy test performed (sensitivity of at least 50 mIU/mL). The test should be performed within the 24 hours prior to beginning thalidomide therapy and then

240 mm

DOMIDE_2IS01114(A05)_Front

720 mm

weekly during the first 4 weeks of use, then at 4 week intervals in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

Neutropenia: (See WARNINGS)

Increased HIV Viral Load: (See WARNINGS)

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: In 10 healthy women, the pharmacokinetic profiles of norethindrone and ethinyl estradiol following administration of a single dose (containing 1.0 mg of norethindrone acetate and 75 µg of ethinyl estradiol) were studied. The results were similar with and without coadministration of thalidomide 200 mg/day to steady-state levels.

Important Non-Thalidomide Drug Interactions

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 and 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 or abstain from heterosexual sexual contact while taking thalidomide.

Carcinogenesis, Mutagenesis, 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 (38-fold greater than the highest recommended daily human dose of 400 mg based upon body surface area [BSA]), 3,000 mg/kg/day to female rats (75-fold the maximum human dose based upon BSA), and 300 mg/kg/day to male rats (7.5-fold the maximum human dose based upon BSA).

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 (AS52/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 dose level including the highest of 100 mg/kg/day to female rabbits and 500 mg/kg/day to male rabbits (approximately 5- and 25-fold the maximum human dose, respectively, based upon BSA). Testicular pathological and histopathological effects (classified as slight) were seen in male rabbits at dose levels ≧ 30mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA).

Pregnancy

Pregnancy Category X (See BOXED WARNING and CONTRANIDICATIONS)

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 heterosexual sexual contact. 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 women can cause birth defects. 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. Any suspected fetal exposure to thalidomide must be reported immediately to health authority.

Because thalidomide is present in the semen of patients receiving the drug, males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential. The risk to the fetus from the semen of male patients taking thalidomide is unknown.

A pre- and postnatal reproductive toxicity study was conducted in pregnant female rabbits. Compound-related increased abortion incidences and elevated fetotoxicity were observed at the lowest oral dose level of 30 mg/kg/day (approximately 1.5-fold the maximum human dose based upon BSA) and all higher dose levels. Neonatal mortality was elevated at oral dose levels to the lactating female rabbits ≧ 150 mg/kg/day (approximately 7.5-fold the maximum human dose based upon BSA). No delay in postnatal development, including learning and memory functions, were noted at the oral dose level to the lactating female rabbits of 150 mg/kg/day (average thalidomide concentrations in milk ranged from 22 to 36 µg/ml).

Use in 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

Of the total number of subjects in this clinical study of thalidomide and dexamethasone combination, 50% ≧ 65 years old and 15% ≧ 75 years old. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitively of some older individuals cannot be ruled out.

【ADVERSE REACTIONS】

The most serious toxicity associated with thalidomide is its documented human teratogenicity. (See BOXED WARNINGS and CONTRAINDICATIONS). The risk of severe birth defects, primarily phocomelia or death to the fetus, is extremely high during the critical period of pregnancy. The critical period is estimated, depending on the source of information, to range from 35 to 50 days after the last menstrual period. The risk of other potentially severe birth defects outside this critical period is unknown, but may be significant. Based on present knowledge, thalidomide must not be used at any time during pregnancy.

Because thalidomide is present in the semen of patients receiving the drug, male receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential.

Thalidomide is associated with drowsiness/somnolence, peripheral neuropathy, dizziness/orthostatic hypotension, neutropenia, and HIV viral load increase (See WARNINGS).

Hypersensitivity to thalidomide and bradycardia in patients treated with thalidomide has been reported (See PRECAUTIONS).

Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide. Thalidomide has been studied in controlled and uncontrolled clinical trials in patients with multiple myeloma and ENL and in people who are HIV-seropositive. In addition, thalidomide has been administered investigationally for more than 20 years in numerous indications. Adverse event profiles from these uses are summarized in the sections that follow.

Other Adverse Events

Due to the longitudinal data were from the basis of this product's safety evaluation, no determination has been made of the causal relationship between the reported adverse events listed below and thalidomide. These lists are of various adverse events noted by investigators in patients to whom they had administered thalidomide under various conditions. The use of thalidomide may not limit disease progression and/or death.

Adverse Events in Multiple Myeloma Controlled Clinical Trial:

The safety analysis was conducted on 204 patients who received study drug in the randomized trial. Table 6 lists the most common treatment-emergent signs and symptoms (occurring at ≧ 10%) that were observed. The most frequently reported adverse events were constipation, sensory neuropathy, confusion, hypocalcemia, edema, dyspnea, thrombosis/embolism, and rash/desquamation (occurring in ≧ 20% of patients and with an increased frequency of ≧ 10% in patients treated with thalidomide/dexamethasone compared with dexamethasone alone).

Twenty-three percent of patients (47/204) discontinued due to adverse events; 30% (31/102) from the thalidomide/dexamethasone arm and 16% (16/102) from the dexamethasone alone arm.

[Table 6] Treatment-Emergent Adverse Events in ≧ 10% of All Patients

Adverse Event (Safety Population; N=204)

Organ System Class/Preferred Term	Thal + Dex (N = 102) All Events [N,(%)]	Thal + Dex Grade 3 Events [N,(%)]	Thal + Dex Grade 4 Events [N,(%)]	Dex alone (N=102) All Events [N,(%)]	Dex alone Grade 3 Events [N,(%)]	Dex alone Grade 4 Events [N,(%)]
Metabolic / Laboratory	97(95.1)	30(29.4)	15(14.7)	96(94.1)	28(27.5)	6(5.9)
Hyperglycemia	74(72.5)	12(11.8)	4(3.9)	81(79.4)	17(16.7)	2(2.0)
Hypocalcemia	73(71.6)	9(8.8)	6(5.9)	60(58.8)	4(3.9)	1(1.0)
Hyponatremia	44(43.1)	11(10.8)	2(2.0)	49(48.0)	13(12.7)	2(2.0)
Hypokalemia	23(22.5)	4(3.9)	1(1.0)	23(22.5)	0(0.0)	1(1.0)
Hyperkalemia	19(18.6)	1(1.0)	2(2.0)	20(19.6)	2(2.0)	0(0.0)
Neurology	92(90.2)	27(26.5)	5(4.9)	76(74.5)	15(14.7)	4(3.9)
Neuropathy-sensory	55(53.9)	3(2.9)	1(1.0)	28(27.5)	1(1.0)	0(0.0)
Confusion	29(28.4)	6(5.9)	3(2.9)	12(11.8)	2(2.0)	3(2.9)
Anxiety / agitation	26(25.5)	1(1.0)	0(0.0)	14(13.7)	3(2.9)	0(0.0)
Tremor	26(25.5)	1(1.0)	0(0.0)	6(5.9)	0(0.0)	0(0.0)
Insomnia	23(22.5)	0(0.0)	0(0.0)	48(47.1)	5(4.9)	0(0.0)
Depression	22(21.6)	2(2.0)	0(0.0)	24(23.5)	1(1.0)	0(0.0)
Neuropathy-motor	22(21.6)	7(6.9)	1(1.0)	16(15.7)	5(4.9)	1(1.0)
Dizziness / lightheadeness	20(19.6)	1(1.0)	0(0.0)	14(13.7)	0(0.0)	0(0.0)
Constitutional Symptoms	91(89.2)	17(16.7)	3(2.9)	84(82.4)	15(14.7)	2(2.0)
Fatigue	81(79.4)	14(13.7)	3(2.9)	72(70.6)	12(11.8)	2(2.0)
Fever	24(23.5)	1(1.0)	0(0.0)	20(19.6)	3(2.9)	0(0.0)
Weight loss	23(22.5)	1(1.0)	0(0.0)	21(20.6)	2(2.0)	0(0.0)
Weight gain	22(21.6)	1(1.0)	0(0.0)	13(12.7)	0(0.0)	0(0.0)
Blood / Bone Marrow	88(86.3)	25(24.5)	9(8.8)	96(94.1)	10(9.8)	10(9.8)
Hemoglobin (decreased)	79(77.5)	13(12.7)	3(2.9)	88(86.3)	5(4.9)	1(1.0)
Leukocytes (decreased)	36(35.3)	6(5.9)	1(1.0)	30(29.4)	1(1.0)	2(2.0)
Neutrophils (decreased)	32(31.4)	8(7.8)	5(4.9)	24(23.5)	3(2.9)	8(7.8)
Platelets (decreased)	24(23.5)	2(2.0)	2(2.0)	34(33.3)	3(2.9)	0(0.0)
Gastrointestinal	83(81.4)	19(18.6)	3(2.9)	70(68.6)	8(7.8)	0(0.0)
Constipation	56(54.9)	8(7.8)	0(0.0)	29(28.4)	1(1.0)	0(0.0)
Anorexia	29(28.4)	4(3.9)	0(0.0)	25(24.5)	2(2.0)	0(0.0)
Nausea	29(28.4)	5(4.9)	0(0.0)	23(22.5)	1(1.0)	0(0.0)
Vomiting	12(11.8)	2(2.0)	0(0.0)	12(11.8)	1(1.0)	0(0.0)
Diarrhea	12(11.8)	1(1.0)	0(0.0)	17(16.7)	3(2.9)	0(0.0)
Dyspepsia	8(7.8)	1(1.0)	0(0.0)	19(18.6)	1(1.0)	0(0.0)
Cardiovascular	70(68.6)	24(23.5)	14(13.7)	60(58.8)	17(16.7)	5(4.9)
Edema	58(56.9)	6(5.9)	0(0.0)	47(46.1)	4(3.9)	0(0.0)
Thrombosis / embolism	23(22.5)	13(12.7)	9(8.8)	5(4.9)	3(2.9)	2(2.0)
Hypotension	16(15.7)	7(6.9)	2(2.0)	15(14.7)	2(2.0)	3(2.9)
Hypertension	11(10.8)	1(1.0)	0(0.0)	12(11.8)	9(8.8)	0(0.0)
Pain	64(62.7)	8(7.8)	2(2.0)	66(64.7)	15(14.7)	0(0.0)
Bone pain	31(30.4)	3(2.9)	2(2.0)	37(36.3)	11(10.8)	0(0.0)
Pain-other	25(24.5)	4(3.9)	0(0.0)	26(25.5)	3(2.9)	0(0.0)
Headache	20(19.6)	3(2.9)	0(0.0)	23(22.5)	0(0.0)	0(0.0)
Myalgia	17(16.7)	0(0.0)	0(0.0)	14(13.7)	1(1.0)	0(0.0)
Arthralgia	13(12.7)	0(0.0)	0(0.0)	10(9.8)	2(2.0)	0(0.0)
Pulmonary	52(51.0)	15(14.7)	6(5.9)	51(50.0)	15(14.7)	5(4.9)
Dyspnea	43(42.2)	10(9.8)	3(2.9)	32(31.4)	12(11.8)	4(3.9)
Cough	15(14.7)	0(0.0)	0(0.0)	19(18.6)	0(0.0)	0(0.0)
Skin	48(47.1)	5(4.9)	1(1.0)	35(34.3)	2(2.0)	0(0.0)
Rash / desquamation	31(30.4)	4(3.9)	0(0.0)	18(17.6)	2(2.0)	0(0.0)
Day skin	21(20.6)	0(0.0)	0(0.0)	11(10.8)	0(0.0)	0(0.0)
Hepatic	47(46.1)	5(4.9)	2(2.0)	45(44.1)	3(2.9)	1(1.0)
Alkaline phosphatase (increased)	27(26.5)	0(0.0)	0(0.0)	29(28.4)	1(1.0)	0(0.0)
SGOT (increased)	25(24.5)	1(1.0)	1(1.0)	24(33.5)	1(1.0)	0(0.0)
Bilirubin (increased)	14(13.7)	1(1.0)	1(1.0)	10(9.8)	1(1.0)	1(1.0)
Renal / Genitourinary	43(42.2)	3(2.9)	3(2.9)	49(48.0)	4(3.9)	3(2.9)
Creatinine	36(35.3)	1(1.0)	1(1.0)	43(42.2)	2(2.0)	2(2.0)
Musculoskeletal	42(41.2)	8(7.8)	2(2.0)	41(40.2)	11(10.8)	3(2.9)
Muscle weakness	41(40.2)	6(5.9)	1(1.0)	38(37.3)	10(9.8)	3(2.9)
Infection / Febrile Neutropenia	23(22.5)	5(4.9)	2(2.0)	28(27.5)	6(5.9)	6(5.9)
Infection without neutropenia	19(17.6)	4(3.9)	1(1.0)	18(17.6)	4(3.9)	2(2.0)

Incidence in ENL Controlled Clinical Trials:

Table 7 lists treatment-emergent signs and symptoms that occurred in thalidomide-treated patients in controlled clinical trials in ENL. Doses ranged from 50 to 300 mg/day. All adverse events were mild to moderate in severity, and none resulted in discontinuation. Table 7 also lists treatment-emergent adverse events that occurred in three of the thalidomide-treated HIV-seropositive patients who participated in an 8-week, placebo-controlled clinical trial. Events that were more frequent in the placebo-treated group are not included.

[Table 7] Summary of Adverse Events (AEs) Reported in Controlled Clinical Trials

Body System / Adverse Event	All AEs In ENL Patients 50-300 mg/day (N=24)	AEs in 3 HIV-seropositive patients: Thalidomide 100 mg/day (N=36)	Thalidomide 200 mg/day (N=32)	Placebo (N=35)
Body as a Whole	16 (66.7%)	18 (50%)	19 (59.4%)	13 (37.1%)
Abdominal pain	1 (4.2%)	1 (2.6%)	1 (3.1%)	4 (11.4%)
Asthenia	2 (8.3%)	2 (5.6%)	7 (21.9%)	1 (2.9%)
Back pain	1 (4.2%)	2 (5.6%)	0	0
Chills	1 (4.2%)	0	3 (9.4%)	4 (11.4%)
Facial edema	1 (4.2%)	0	0	0
Fever	0	7 (19.4%)	7 (21.9%)	6 (17.1%)
Headache	3 (12.5%)	6 (16.7%)	6 (18.7%)	4 (11.4%)
Infection	0	3 (8.3%)	2 (6.3%)	1 (2.9%)
Malaise	2 (8.3%)	0	0	0
Neck pain	1 (4.2%)	0	0	0
Neck rigidity	1 (4.2%)	0	0	0
Pain	2 (8.3%)	0	1 (3.1%)	2 (5.7%)
Digestive System	5 (20.8%)	16 (44.4%)	16 (50%)	15 (42.9%)
Anorexia	0	1 (2.8%)	3 (9.4%)	2 (5.7%)
Constipation	1 (4.2%)	1 (2.8%)	3 (9.4%)	0
Diarrhea	1 (4.2%)	4 (11.1%)	6 (18.7%)	6 (17.1%)
Dry mouth	0	3 (8.3%)	3 (9.4%)	2 (5.7%)
Flatulence	0	3 (8.3%)	0	2 (5.7%)
Liver function tests abnormalities	0	0	3 (9.4%)	0
Nausea	1 (4.2%)	0	4 (12.5%)	1 (2.9%)
Oral moniliasis	1 (4.2%)	4 (11.1%)	2 (6.3%)	0
Tooth pain	1 (4.2%)	0	0	0
Hemic and Lymphatic	0	8 (22.2%)	13 (40.6%)	10 (28.6%)
Anemia	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Leukopenia	0	6 (16.7%)	8 (25%)	3 (8.6%)
Lymphadenopathy	0	2 (5.6%)	4 (12.5%)	3 (8.6%)
Metabolic and Endocrine Disorders	1 (4.2%)	8 (22.2%)	12 (37.5%)	8 (22.9%)
Edema peripheral	1 (4.2%)	3 (8.3%)	1 (3.1%)	0
Hyperlipemia	0	2 (5.6%)	3 (9.4%)	1 (2.9%)
SGOT increased	0	1 (2.8%)	4 (12.5%)	2 (5.7%)
Nervous System	13 (54.2%)	19 (52.8%)	18 (56.3%)	12 (34.3%)
Agitation	0	0	3 (9.4%)	0
Dizziness	1 (4.2%)	7 (19.4%)	6 (18.7%)	0
Insomnia	0	0	3 (9.4%)	2 (5.7%)
Nervousness	0	1 (2.8%)	3 (9.4%)	0
Neuropathy	0	3 (8.3%)	0	0
Paresthesia	0	2 (5.6%)	5 (15.6%)	4 (11.4%)
Somnolence	9 (37.5%)	13 (36.1%)	12 (37.5%)	4 (11.4%)
Tremor	1 (4.2%)	0	0	0
Vertigo	2 (8.3%)	0	0	0
Respiratory System	3 (12.5%)	9 (25.0%)	6 (18.7%)	9 (25.7%)
Pharyngitis	1 (4.2%)	3 (8.3%)	2 (6.3%)	2 (5.7%)
Rhinitis	1 (4.2%)	0	0	4 (11.4%)
Sinusitis	1 (4.2%)	3 (8.3%)	1 (3.1%)	2 (5.7%)
Skin and Appendages	10 (41.7%)	17 (47.2%)	18 (56.3%)	19 (54.3%)
Acne	0	4 (11. 1%)	1 (3.1%)	0
Dermatitis fungal	1 (4.2%)	2 (5.6%)	3 (9.4%)	0
Nail disorder	1 (4.2%)	0	1 (3.1%)	0
Pruritus	2 (8.3%)	1 (2.8%)	2 (6.3%)	2 (5.7%)
Rash	5 (20.8%)	9 (25.0%)	8 (25.0%)	11 (31.4%)
Rash maculo-papular	1 (4.2%)	6 (16.7%)	6 (18.7%)	2 (5.7%)
Sweating	0	0	4 (12.5%)	4 (11.4%)
Urogenital System	2 (8.3%)	6 (16.7%)	2 (6.3%)	4 (11.4%)
Albuminuria	0	3 (8.3%)	1 (3.1%)	2 (5.7%)
Hematuria	0	4 (11.1%)	0	1 (2.9%)
Impotence	2 (8.3%)	1 (2.8%)	0	0

Other Adverse Events Observed in ENL Patietns

Thalidomide in doses up to 400 mg/day has been administered investigationally in the United Stated over a 19-year period in 1465 patients with ENL. The published literature describes the treatment of an additional 1678 patients. To provide a meaningful estimate of the proportion of the individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using a modified COSTART dictionary/terminology. These categories are used in the listing below. All reported events are included except those already listed in the previous table. Due to the fact that these data were collected from uncontrolled studies, the incidence rate cannot be determined. As mentioned previously, no causal relationship between thalidomide and these events can be conclusively determined at this time. These are reports of all adverse events noted by investigators in patients to whom they had administered thalidomide.

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

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

Digestive System: Anorexia, appetite increase/weight gain, dry mouth, dyspepsia, enlarged liver, eructation, flatulence, increased liver function tests, 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, amyloidosis, bilirubinemia, BUN increased, creatinine increased, 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.

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, sweating, urticaria, vesiculobullous rash.

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

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

Other Adverse Events Observed in HIV-seropositive Patients

In addition to controlled clinical trials, thalidomide has been used in uncontrolled studies in 145 patients. Less frequent adverse events that have been reported in these HIV-seropositive patients were grouped into a smaller number of standardized categories using a modified COSTART dictionary/terminology and these categories are used in the listing below. Adverse events that have already been included in the tables and narrative above, or that are too general to be informative are not listed.

Body as a Whole: Ascites, AIDS, allergic reaction, cellulitis, chest pain, chills and fever, cyst, decreased CD4 count, facial edema, flu syndrome, hernia, thyroid hormone level altered, moniliasis, photosensitivity reaction, sarcoma, sepsis, viral infection.

Cardiovascular System: Angina pectoris, arrhythmia, atrial fibrillation, bradycardia, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, heart arrest, heart failure, hypertension, hypotension, murmur, myocardial infarct, palpitation, pericarditis, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis.

Digestive System: Cholangitis, cholestatic jaundice, colitis, dyspepsia, dysphagia, esophagitis, gastroenteritis, gastrointestinal disorder, gastrointestinal hemorrhage, gum disorder, hepatitis, pancreatitis, parotid gland enlargement, periodontitis, stomatitis, tongue discoloration, tooth disorder.

Hemic and Lymphatic: Aplastic anemia, macrocytic anemia, megaloblastic anemia, microcytic anemia.

Metabolic and Endocrine: Avitaminosis, bilirubinemia, dehydration, hypercholesteremia, hypoglycemia, increased alkaline phosphatase, increased lipase, increased serum creatinine, peripheral edema.

Muscular Skeletal: Myalgia, myasthenia.

Nervous System: Abnormal gait, ataxia, decreased libido, decreased reflexes, dementia, dysesthesia, dyskinesia, emotional lability, hostility, hypalgesia, hyperkinesia, incoordination, meningitis, neurologic disorder, tremor, vertigo.

Respiratory System: Apnea, bronchitis, lung disorder, lung edema, pneumonia (including Pneumocystis carinii pneumonia), rhinitis.

Skin and Appendages: Angioedema, benign skin neoplasm, eczema, herpes simplex, incomplete Stevens-Johnson syndrome, nail disorder, pruritus, psoriasis, skin discoloration, skin disorder.

Special Senses: Conjunctivitis, eye disorder, lacrimation disorder, retinitis, taste perversion.

Other Adverse Events Observed in Post-Marketing Use

Cardiovascular System: Cardiac arrhythmias including atrial fibrillation, bradycardia, tachycardia, sick sinus syndrome and EKG abnormalities.

Digestive System: Intestinal perforation.

Metabolic and Endocrine: Electrolyte imbalance including hypercalcemia or hypocalcemia, hyperkalemia and hypokalemia, hyponatremia, hypothyroidism, and increased alkaline phosphatase, tumor lysis syndrome.

Nervous System: 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 epilepicus.

Skin and Appendages: Erythema multiforme.

Hemic and Lymphatic: Decreased white blood cell counts including neutropenia and febrile neutropenia, changes in prothrombin time.

Respiratory System: Pleural effusion.

Other Adverse Events in the Published Literature or Reported from Other Sources

The following additional events have been identified either in the published literature or from spontaneous reports from other sources: acute renal failure, pulmonary hypertension, 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, viral infections, including herpes zoster and hepatitis B virus reactivation, lymphopenia, metrorrhagia, migraine, myxedema, nodular sclerosing Hodgkin's disease, nystagmus, oliguria, pancytopenia, petechiae, purpura, Raynaud's syndrome, stomach ulcer, and suicide attempt.

【DRUG ABUSE AND DEPENDENCE】

Physical and psychological dependence has not been reported in patients taking thalidomide. But it should be avoided to be used abusively as hypnotics by patients. However, as with other tranquilizers/hypnotics, thalidomide too has been reported to create in patients habituation to its soporific effects.

【OVERDOSAGE】

There have been three cases of overdose reported, all attempted suicide. There have been no reported fatalities in doses of up to 14.4 grams, and all patients recovered without reported sequelae.

【POSOLOGY AND METHOD OF ADMINISTRATION】

- DOMIDE must only be administered in compliance with all the instructions outlined in the informed consent form. Drugs prescribed to women of childbearing potential must be contingent upon initial and continued confirmed negative results of pregnancy testing.
- Thalidomide treatment must be initiated and monitored under the supervision of physicians with expertise in managing immunomodulatory or chemotherapeutic agents and a full understanding of the risks of thalidomide therapy and monitoring requirements.
- To reduce central nervous system effects (e.g. drowsiness, somnolence, sedation) during the day, thalidomide is normally taken as a single dose in the evening. Thalidomide capsules should be taken at least one hour after food.

**** Multiple Myeloma***

- The required total duration of treatment should be individually determined for each patient depending on tolerability and disease progression.

- In combination with Melphalan and Prednisone:

The DOMIDE recommended oral dose is 200 mg per day. A maximum number of 12 cycles of 6 weeks (42 days) should be used.

- In combination with Dexamethasone:

The DOMIDE recommended oral dose is 200 mg per day. For induction, 4 cycles of 4 weeks (28 days) of thalidomide/dexamethasone is recommended. The dose of dexamethasone is 40 mg daily administered orally on days 1-4, 9-12, and 17-20 every 28 days.

- Patients who develop side effects such as constipation, oversedation, or peripheral neuropathy may benefit by either temporarily discontinuing the drug or continuing at a lower dose. With the abatement of these side effects, the drug may be started at a lower dose or at the previous dose based on clinical judgment
- For elderly patients of poor performance, tolerability may be improved by starting the patient on 50 mg per day and increasing this dose to 200 mg per day over a 4 week period.

**** Erythema Nodosum Leprosum (ENL)***

- For an episode of cutaneous ENL, DOMIDE dosing should be initiated at 100 to 300 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after 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, DOMIDE dosing may be initiated at higher doses up to 400 mg/day once daily at bedtime or divided doses with water, at least 1 hour after meals.
- In patients with moderate to severe neuritis associated with severe ENL reaction, corticosteroids may be started concomitantly with DOMIDE. Steroid usage can be tapered and discontinued when the neuritis has ameliorated.
- Dosing with DOMIDE 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.
- There have been no well-controlled studies of thalidomide as maintenance therapy to prevent ENL relapse to provide maintenance dosing recommendations. 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.
- Patients should not take double doses of DOMIDE in one time, when patients miss the previous dose. In case, patients miss one dose of DOMIDE, patients should make up as soon as possible but the timing of dose making up should not be close to the next dose.

**** Dosage adjustments during treatment***

Dosage delay or reduction, dependent upon grade of toxicity, may be necessary.

-Thromboembolic Events

Thromboprophylaxis should be administered for at least the first 5 months of treatment, especially in patients with additional thrombotic risk factors. Prophylactic antithrombotic medicinal products, such as low molecular weight heparins or warfarin, should be recommended. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

- If the patient experiences any thromboembolic events during treatment with thalidomide in combination, discontinue treatment and start standard anticoagulation therapy. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the thalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of thalidomide treatment

-Peripheral Neuropathy

If the patient experiences peripheral neuropathy during treatment with thalidomide in combination, treatment should be discontinued. Continue to monitor the patient and when the patient reaches Grade 1 neuropathy, the treatment may be restarted at a 50% reduction. If at any time the patient experiences Grade 3 or 4 neuropathy, the treatment should be discontinued permanently.

-Patients with renal or hepatic impairment

No specific studies have been conducted in patients with renal or hepatic impairment. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.

【COMPOSITION】

Each capsule contains 50 mg thalidomide.

【PACKAGE】

60 capsules in PTP box.

【STORAGE】

Please store below 30°C.

Avoid heat, moisture and direct light exposure. Please keep out of the reach of children.

【EXPIRATION】

See the label on carton.

【MANUFACTURER】

TTY Biopharm Company Limited

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【Name and Address of marketing authorization】

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【Date of revision】

23 Apr 2025

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240 mm

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