DOMIDE Capsules 50 mg

Thalidomide 50 mg

【BOXED WARNINGS】

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 or could become pregnant within 4 weeks after stopping the medicine. 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 Letter of consent 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.

VENOUS THROMBOEMBOLISM

The use of Thalidomide in combination with standard chemotherapeutic agents including dexamethasone in multiple myeloma results in an increased risk of venous thromboembolism, such as deep venous thrombosis and pulmonary embolism. 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.

【INDICATION】

Multiple Myeloma (MM):

- 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.

【POSOLOGY AND METHOD OF ADMINISTRATION】

- 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. DOMIDE capsules should be taken at least one hour after food.

Multiple Myeloma (MM)

- The required total duration of treatment should be individually determined for each patient depending on tolerability and disease progression.
- Depending on tolerance and observed toxicity, lower maintenance doses can be used.

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.
- For patients > 75 years of age, the DOMIDE recommended starting dose is 100 mg per day

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.
- 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.

Dosage Adjustments During Treatment

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

If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

-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, 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 anytime 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.

-Elderly Population

- No specific dose adjustments are recommended for the elderly

≤ 75 years of age. For patients > 75 years of age, the Thalidomide recommended starting dose is 100 mg per day.

-Paediatric Population

- There is no relevant use of Thalidomide in the paediatric population in the indication of multiple myeloma.

【CONTRAINDICATIONS】

DOMIDE are contraindicated in the following patients:

- Hypersensitivity to Thalidomide or to any of the excipients
- Pregnant women, or those who are breastfeeding
- Women of child bearing potential who are not using, not willing or not able to use adequate contraceptive measures to prevent pregnancy
- Women of childbearing potential where there is an alternative treatment of non-inferior efficacy available
- Males who are not able or willing to comply with adequate contraceptive measures

【WARNINGS AND PRECAUTIONS】

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.

Females of Reproductive Potential

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, two other effective or highly effective methods may be used.

Pregnancy Testing

Women of childbearing potential being treated with Thalidomide should have a pregnancy test (sensitivity of at least 25 mIU/mL), and a prescription must not be issued until a written report of a negative pregnancy test has been obtained by the prescriber.

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when thalidomide is prescribed or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with thalidomide.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

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.

Male Patients

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 (women who have not undergone hysterectomy or who have not been post-menopausal for at least 1 year).

Condom use should continue for 4 weeks after cessation of Thalidomide treatment. In the case of a male patient with an allergy to latex or polyurethane, at least one highly efficacious method should be used by any female sexual partner. Contraception should be started in this partner at least 4 weeks prior to the start of a sexual relationship with the patient, and continued throughout Thalidomide treatment and for an additional 4 weeks following cessation of treatment.

The risk to the fetus from the semen of male patients taking Thalidomide is unknown.

Male patients must not donate sperm whilst taking DOMIDE and for 4 weeks after cessation treatment.

Blood Donation

Patients must not donate blood during treatment with DOMIDE 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 Thalidomide.

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.

Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.

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) and arterial thromboembolism

(such as myocardial infarction and cerebrovascular event). The risk appears to be greatest during the first 5 months of therapy.

Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Risk factors associated with arterial thrombotic events, in addition to the underlying malignant disease, age ≥65 years and being male, included hyperlipidaemia, hypertension, diabetes, obesity, renal disease, and tobacco use.

This risk increases significantly when Thalidomide is used in combination with standard chemotherapeutic agents including melphalan, prednisone or 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). Thromboprophylaxis and dosing/anticoagulation therapy measures should be followed based on a careful assessment of an individual patient's underlying risk factors. All Thalidomide-treated patients should be monitored for thromboembolic events. If a patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy should be started.

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.

Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone:

In two randomized clinical trials in patients with MM, the addition of pembrolizumab to a Thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a Thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Myocardial Infarction:

Myocardial infarction (MI) has been reported in patients receiving Thalidomide, particularly in those with known risk factors. Patients with known risk factors for MI, including prior thrombosis, should be closely monitored and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia)

Drowsiness and Somnolence:

Thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid situations where drowsiness may be a problem and not to take other medications that may cause drowsiness without adequate medical advice. Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.

Peripheral Neuropathy:

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a very 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. Incidence of neuropathy events leading to discontinuation, dose reduction or interruption increases with cumulative dose and duration of therapy. 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 ENL 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 DOMIDE 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, DOMIDE 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.

Syncope, bradycardia and atrioventricular block:

Patients should be monitored for syncope, bradycardia and atrioventricular block; dose reduction or discontinuation may be required.

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.

Haematological Disorders: Neutropenia and Thrombocytopenia:

Neutropenia or thrombocytopenia, including Grade 3 or 4 occurrences for both events, has been reported in association with the clinical use of Thalidomide in combination with melphalan and prednisone. For Thalidomide in combination with other medicines, treatment should be initiated with caution in patients with neutropenia, in accordance with oncology guidelines.

Patients should be monitored and dose reduction, delay or discontinuation may be required. White blood cell count and differential count should be monitored on an on-going basis, especially in patients who may be more prone to neutropenia, such as those with myeloma or those who are HIV-seropositive. If ANC decreases to below 750/mm^3 (0.75 x 10^9/L) while on treatment, the patient's medication regimen should be re-evaluated and consideration should be given to withholding DOMIDE if clinically appropriate.

Patients and physicians are advised to be observant for signs and symptoms of bleeding including petechiae, epistaxis and gastrointestinal bleeding, especially in case of concomitant medication susceptible to induce bleeding.

Allergic Reactions and Serious Skin Reactions:

Angioedema and serious dermatological reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events can be fatal.

Thalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Thalidomide must be discontinued for angioedema, anaphylactic reactions, Grade 4 rash, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected and should not be resumed following discontinuation for these reactions. Rechallenge in some treatment populations e.g. HIV patients, has produced a severe and immediate reaction associated with fever, tachycardia, hypotension and rash.

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.

Drowsiness, Somnolence and Sedation:

Thalidomide frequently causes drowsiness, somnolence and sedation. 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 reduction may be required. Thalidomide may potentiate the drowsiness caused by alcohol. As with any sedative medication, the potential for impaired consciousness may increase the risk for aspiration of food, vomitus and oral secretions.

Patients should be advised as to the possible impairment of mental and/or physical abilities required for the performance of hazardous tasks.

Tumour Lysis Syndrome:

The patients at risk of tumour lysis syndrome are those with a high tumour burden prior to treatment.

These patients should be monitored closely and appropriate precautions taken.

Infections:

Patients should be monitored for severe infections including sepsis and septic shock.

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

Progressive Multifocal Leukoencephalopathy (PML):

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with thalidomide in combination with immunosuppressive therapy including dexamethasone. PML was reported several months to several years after starting the treatment with thalidomide. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive or behavioural signs or symptoms and appropriate diagnostic measures for PML are recommended.

If PML is suspected, further thalidomide dosing must be suspended until PML has been excluded. If PML is confirmed, thalidomide must be permanently discontinued.

Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndromes (MDS):

AML and MDS were observed in one clinical trial in patients with previously untreated MM receiving the combination of melphalan, prednisone, and Thalidomide (MPT).

Take into account both the benefit achieved with Thalidomide and the risk of AML and MDS before initiating treatment with Thalidomide in combination with melphalan and prednisone (MPT). Carefully evaluate patients before and during treatment using standard cancer screening and institute treatment as indicated.

Seizures:

Although very rare, seizures, including generalised clonic/tonic convulsions, have been reported during use of Thalidomide. Most of the patients had disorders that may have predisposed 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.

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.

Posterior reversible encephalopathy syndrome (PRES)/ Reversible posterior leukoencephalopathy syndrome (RPLS)

Cases of PRES/RPLS have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The majority of the reported cases had recognized risk factors for PRES/RPLS, including hypertension, renal impairment and concomitant use of high dose corticosteroids and/or chemotherapy.

Lactose Intolerance:

The DOMIDE 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.

【 INTERACTIONS WITH OTHER MEDICINES AND OTHER

FORMS OF INTERACTIONS】(from literature)

Drug Interactions:

Thalidomide is not extensively metabolised by cytochrome P450 isoenzymes. Thalidomide does not inhibit the following human cytochrome P450 enzymes in vitro at clinically-relevant concentrations: CYP1A2, 2B6, 2C9, 2C19, 2D6, 2E1 and 3A4. Thalidomide does not induce the following human cytochrome P450 enzymes in vitro at clinically-relevant concentrations: CYP1A2, 2B6, 2C9, 2C19 and 3A4/5. Thalidomide is neither a substrate nor an inhibitor of P-glycoprotein. Therefore, pharmacokinetic drug interactions involving induction or inhibition of CYPP450 enzymes or P-glycoprotein are considered unlikely during clinical use.

Interactions between DOMIDE and other medicines have not been extensively studied.

Increase of Sedative Effects of Other Medicines:

Thalidomide has been reported to enhance the sedative activity of barbiturates, alcohol, chlorpromazine, and reserpine. Thalidomide increases the effects of morphine derivatives, benzodiazepines, other anxiolytics, hypnotics, sedative antidepressants, neuroleptics, sedative H1 antihistamines, central antihypertensives, and baclofen.

Bradycardic Effect:

Due to Thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as beta blockers, anticholinesterase agents, or active substances known to induce torsade de pointes.

Peripheral Neuropathy:

Medications known to be associated with peripheral neuropathy (e.g. zalcitabine, vincristine, and didanosine) should be used with caution in patients receiving Thalidomide.

Cytotoxic Medicines:

An increased risk for thrombosis and thromboembolic events has been reported in association with the use of Thalidomide in combination with cytotoxic medicines e.g. doxorubicin and melphalan.

Oral Contraceptives*:*

Thalidomide does not interact with 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. However, caution should be exercised when combined hormonal contraceptives are used during treatment with Thalidomide due to the increased risk of venous thromboembolic disease.

Concomitant Therapies that May Increase the Risk of Thromboembolism:

Erythropoietic agents, or other agents that may increase the risk of thromboembolism, such as oestrogen containing therapies, should be used with caution in multiple myeloma.

Warfarin:

Thalidomide does not interact with warfarin. In 13 healthy male volunteers, multiple dose administration of 200 mg Thalidomide had no effect on the single dose pharmacokinetics of warfarin (both S-warfarin and R-warfarin), and had no effect on the international normalized ratio (INR). In addition, single dose administration of 25 mg warfarin had no effect on Thalidomide pharmacokinetics.

Digoxin:

Thalidomide does not interact with digoxin. In 18 healthy male volunteers, multiple dose administration of 200 mg Thalidomide had no apparent effect on the single dose pharmacokinetics of digoxin. In addition, single dose administration of 0.5 mg digoxin had no apparent effect on Thalidomide pharmacokinetics.

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.

【FERTILITY, PREGNANCY AND LACTATION】(from literature)

Thalidomide is a known human teratogen and should not, under any circumstances, be administered during pregnancy, or to women of childbearing potential, unless they are using at least one effective means of contraception. A single dose taken by pregnant women can cause birth defects. Major human foetal abnormalities related to thalidomide administration during pregnancy are: amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), facial palsy, eye abnormalities (anopthalmos, micropthalmos), and congenital heart defects. Alimentary tract, urinary tract and genital malformations have also been documented. Mortality at or shortly after birth has been reported at or about
40%

Breast-Feeding

It is not known whether Thalidomide is excreted in human milk. Thalidomide has been detected in the milk of lactating rabbits given Thalidomide by oral gavage, at concentrations up to 3.6 times maternal plasma levels. Women who are taking thalidomide should not breast feed.

Fertility

A study in rabbits demonstrated no effect on fertility indices in males or females although testicular degeneration was observed in males.

【EFFECTS ON ABILITY TO DRIVE AND USE MACHINES】

Thalidomide may cause sedation, drowsiness, somnolence and orthostatic hypotension. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks while being treated with DOMIDE

【ADVERSE REACTIONS】(from literature)

Nearly all patients can be expected to experience adverse reactions. The most commonly observed adverse reactions associated with the use of Thalidomide in combination with dexamethasone or melphalan and prednisone are: deep vein thrombosis, constipation, peripheral oedema, tremor, dizziness, fatigue, somnolence, peripheral neuropathy, neutropenia, lymphopenia, leukopenia, anaemia, thrombocytopenia, paraesthesia, and dysaesthesia.

Untreated Multiple Myeloma in Combination Therapy

The clinically important adverse reactions associated with the use of Thalidomide in combination include: deep vein thrombosis and pulmonary embolism, peripheral neuropathy, bradycardia, orthostatic hypotension, dizziness, syncope, and severe skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

In a study where subjects in the control arm received Thalidomide in combination with melphalan and prednisone, the adverse event profile reported in subjects > 75 years of age treated with Thalidomide 100 mg once daily was similar to the adverse event profile observed in subjects ≤ 75 years of age in patients treated with Thalidomide 200 mg once daily. However, due to additional co-morbidities and risk factors, patients with age > 75 years are potentially at risk for a higher frequency of serious adverse events.

Table 1 and Table 2 contain only the adverse events for which a causal relationship with medicine treatment could reasonably be established. Frequencies given are based on the observations during pivotal comparative clinical studies investigating the effect of Thalidomide in combination with melphalan and prednisone, and with dexamethasone in previously untreated multiple myeloma patients (Table 1 and Table 2, respectively). Additional adverse events related to Thalidomide and not seen in either pivotal study are based on post-marketing experience with the medicine.

Frequencies are defined as:

- very common > 1/10;
- common > 1/100, < 1/10;
- uncommon > 1/1000, < 1/100;
- rare > 1/10,000, < 1/1000;
- very rare < 1/10,000 including isolated reports.

Table 1: Thalidomide in Combination with Melphalan and Prednisone

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very Common	Neutropenia, Leukopenia, Anaemia, Lymphopenia, Thrombocytopenia
Cardiac disorders	Common	Cardiac failure, Bradycardia
Gastrointestinal disorders	Very Common	Constipation
	Common	Vomiting, Dry mouth
General disorders and administration site conditions	Very Common	Peripheral edema,
	Common	Pyrexia, Asthenia, Malaise
Infections and infestations	Common	Pneumonia
Nervous system disorders	Very Common	Peripheral neuropathy, Tremor, Dizziness, Somnolence, Paraesthesia, Dysaesthesia
	Common	Abnormal coordination
Psychiatric disorders	Common	Depression, Confusional state
Respiratory, thoracic and mediastinal disorders	Common	Pulmonary embolism, Dyspnoea, Bronchopneumopathy, Interstitial lung disease
Skin and subcutaneous	Common	Toxic skin eruption, Dry skin, Rash
Vascular disorders	Common	Deep vein thrombosis

Table 2: Thalidomide in Combination with Dexamethasone

System Organ Class	Frequency	Adverse reaction
Cardiac disorders	Common	Bradycardia
Eye disorders	Common	Blurred vision
Ear and labyrinth disorders	Common	Vertigo
Gastrointestinal disorders	Very Common	Constipation
	Common	Vomiting, Nausea, Dyspepsia, Dry mouth
	Uncommon	Peritonitis, Diverticular perforation
General disorders and administration site conditions	Very Common	Peripheral edema, Fatigue
	Common	Pyrexia, Asthenia
Infections and infestations	Common	Pneumonia
Musculoskeletal, connective tissue and bone disorders	Common	Muscle cramps
Nervous system disorders	Very Common	Peripheral neuropathy, Tremor,Dizziness
	Common	Transient ischaemic event, Ataxia, Syncope, Paraesthesia ,Somnolence
	Uncommon	Cerebrovascular accident
Psychiatric disorders	Common	Mood alteration, Depression, Anxiety, Confusional state
Respiratory, thoracic and mediastinal disorders	Common	Pulmonary embolism
	Uncommon	Bronchitis
Skin and subcutaneous	Common	Rash
Vascular disorders	Very Common	Deep vein thrombosis
	Common	Hypotension
	Uncommon	Orthostatic hypotension

Adverse reactions for haematological disorders are provided compared to the comparator arm as the comparator has a significant effect on these disorders (Table 3).

Table 3: Comparison of Grade 3 and 4 Haematological Disorders for MP and MPT Combinations and the Thal/Dex and Placebo/Dex Combinations

Study	IFM 99-06	THAL-MM-003

	n (% of patients)		n (% of patients)	
Treatment Arm	MP (n=193)	MPT (n=124)	Placebo/Dex (n=232)	Thal/Dex (n=234)
Neutropenia	57 (29.5)	53 (42.7)	3 (1.3)	7 (3.0)
Leukopenia	32 (16.6)	32 (25.8)	1 (0.4)	4 (1.7)
Anaemia	28 (14.5)	17 (13.7)	1 (0.4)	0
Lymphopenia	14 (7.3)	15 (12.1)	0	0
Thrombocytopenia	19 (9.8)	14 (11.3)	0	0

Description of Selected Adverse Reactions

Teratogenicity

The most serious toxicity associated with Thalidomide is teratogenicity. 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 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.

Thalidomide must not be used at any time during pregnancy.

Thromboembolic Events

An increased risk of venous thromboembolic events such as deep venous thrombosis (DVT) and pulmonary embolus (PE) and arterial thromboembolism (such as myocardial infarction and cerebrovascular events) has been reported in patients treated with Thalidomide.

Peripheral Neuropathy

Peripheral neuropathy is a very common, potentially severe, adverse effect of treatment with Thalidomide that may result in irreversible damage.

Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short-term use also exist. Incidence of neuropathy events leading to discontinuation, dose reduction or interruption increases with cumulative dose and duration of therapy. Symptoms may occur some time after Thalidomide treatment has been stopped and may resolve slowly or not at all.

Monitoring during Thalidomide treatment should include regular SNAP assessments.

Post-Marketing Data

Additional adverse events related to post-marketing experience with Thalidomide and not seen in pivotal and supportive studies include:

Blood and Lymphatic System Disorders: Febrile neutropenia, pancytopenia

Cardiac Disorders: Myocardial infarction

Endocrine Disorders: Hypothyroidism

Gastrointestinal Disorders: Intestinal obstruction, gastrointestinal perforation, gastrointestinal hemorrhage

Hepatobiliary Disorders: Hepatic disorders (mainly abnormal liver function tests)

Immune System Disorders: Allergic reactions (hypersensitivity, angioedema, urticaria)

Infections and Infestations: Severe infections (fatal sepsis including septic shock) viral infections (including herpes zoster and hepatitis B virus reactivation)

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Tumour lysis syndrome

Nervous System Disorders: Convulsions

Reproductive System and Breast Disorders: Sexual dysfunction, menstrual disorders including amenorrhea

Respiratory, Thoracic and Mediastinal Disorders: Pulmonary hypertension, pulmonary embolism

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)

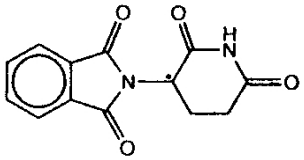
【OVERDOSE】

Eighteen cases of overdose have been reported in the literature concerning doses up to 14.4 g. No fatalities have been reported and all overdose patients recovered without sequelae. There is no specific antidote for a Thalidomide overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure and respiratory status.

【DESCRIPTION】

Each DOMIDE capsule contains 50 mg of active ingredient, thalidomide. The appearance of capsules is hard capsules, and white body orange cap.

Thalidomide, α-(N-phthalimido) glutarimide, is an immunomodulatory agent. The empirical formula is $C_{13}H_{10}N_2O_4$, and the grammolecular 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:

Microcrystalline Cellulose pH-l02; Lactose Monohydrate; Lactose spray-dried; Corn starch; Colloidal Silicon Dioxide; Stearic acid; Magnesium stearate.

The Lactose Monohydrate, Lactose spray-dried and hard capsule shell are from bovine source.

【PHARMACOLOGICAL PROPERTIES】(from literature)

Pharmacotherapeutic group: immunosuppressants, other

immunosuppressants, ATC code: L04AX02.

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.

Thalidomide does not consistently reduce TNF-α level in all disease states, and, in fact, thalidomide may increase TNF-α levels in some clinical indications. It should be noted that the use of thalidomide to reduce TNF-α levels in a group of patients with toxic epidermal necrolysis, resulted in an unexpected increase in TNF-α levels and considerably increased mortality compared to placebo.

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.

Clinical trials

Untreated Multiple Myeloma:

Results from IFM 99-06, a phase III, randomised, open label, parallel group, multicentre study have demonstrated a survival advantage when Thalidomide is used in combination with melphalan and prednisone (MPT) in the treatment of newly diagnosed multiple myeloma patients. In this study, the age range of patients was 65-75 years, with 41% (183/447) of patients 70 years old or older. The median dose was 200 mg and > 40% of patients received 9 cycles.

Treatment with MPT was associated with improved overall survival (OS) compared to treatment with melphalan and prednisone (MP) alone (hazard ratio 0.56, 97.5% CI: 0.37 - 0.84; p = 0.0012). Median overall survival was prolonged – 53.6 months with MPT compared to 32.2 months with MP.

An update to overall survival was conducted for the IFM 99-06 study providing an additional 15 months follow-up data. The OS advantage was maintained with updated median survival times of 51.6 ± 4.5 and 33.2 ± 3.2 months in the MPT and MP groups, respectively (97.5% CI: 0.42 - 0.84).

Study MM-003 was a phase III, randomised, parallel group, double-blind, placebo-controlled multicenter study which compared the combination of thalidomide and dexamethasone (Thal/Dex) with placebo and dexamethasone. The Thal/Dex combination was associated with a significant improvement in time to disease progression (hazard ratio 0.43, 95% CI: 0.32 – 0.58; p < 0.0001). Median time to progression was prolonged from 28.3 weeks with placebo/dexamethasone group to 97.7 weeks with Thal/Dex. Progression-free survival (PFS) was also significantly improved (hazard ratio 0.50, 95% CI: 0.38 – 0.64; p < 0.0001; median PFS 64.4 versus 28.0 weeks). Overall response rate was also significantly greater (63% versus 46%). No improvement in overall survival was demonstrated.

Study E1A00 was a phase III, randomised, parallel group, open-label, multicentre study conducted by the US Eastern Co-operative Oncology Group to study the combination of Thal/Dex versus Placebo/Dex in 200 previously untreated MM patients. The primary endpoint was overall response at 4 months defined as a decrease in serum and urine M-protein of ≧ 50%. The response rate with Thal/Dex was significantly higher than with dexamethasone alone: 61/99 (61.6%) versus 41/101 (39.6%), respectively, (p = 0.001).

【PHARMACOKINETIC PROPERTIES】

Absorption：

The absolute bioavailability of thalidomide capsules has not yet been obtained in human subjects due to its poor aqueous solubility. Based on the ^{14}C-radiolabel thalidomide study in human, greater than 90% of the total radioactivity is recovered in urine suggesting good oral absorption.

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 4 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 4: 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：

In a ^{14}C radiolabel study in humans, unchanged medicine is the predominant circulating component. Thalidomide is not metabolised to any significant extent by the liver cytochrome P450 system.

Unchanged Thalidomide is not eliminated by the kidney to a notable degree (< 3.5% of the dose), but is primarily excreted as hydrolytic metabolites in urine.

Elimination：

The mean elimination half-life of thalidomide in plasma following single oral doses between 50 mg and 400 mg was 5.5 to 7.3 hours. Following a single oral dose of 400 mg of radio-labelled Thalidomide, the total mean recovery was 93.6 % of the administered dose by day 8. The majority of the radioactive dose was excreted within 48 hour following dose administration. The major route of excretion was via the urine (> 90 %) while faecal excretion was minor.

There is a linear relationship between body weight and estimated Thalidomide clearance; in multiple myeloma patients with body weight from 47-133 kg, Thalidomide clearance ranged from approximately 6-12 L/h, representing an increase in thalidomide clearance of 0.621 L/h per 10 kg body weight increase.

【PRECLINICAL SAFETY DATA】

Genotoxicity

Thalidomide was negative in tests for mutagenicity in Salmonella typhimurium, Escherichia coli and Chinese hamster ovary cells in vitro, and did not induce micronuclei in the bone marrow of mice.

Carcinogenicity

Thalidomide showed no evidence of carcinogenicity in 104-week oral gavage studies in mice administered 0, 100, 1000 or 3000 mg/kg/day (respective systemic exposures up to approximately 4 times the estimated clinical AUC at the maximum dose of 800 mg/day), male rats administered 0, 20, 160 or 300 mg/kg/day (respective exposures up to approximately 4 times the estimated clinical AUC at the maximum dose) or female rats administered 0, 30, 300 or 3000 mg/kg/day (respective exposures up to approximately 11 times the estimated clinical AUC at the maximum dose).

【COMPOSITION】

Each DOMIDE capsule contains 50 mg Thalidomide

Excipients

Microcrystalline Cellulose pH 102, Lactose Monohydrate, Lactose spray-dried, Corn starch, Colloidal Silicon Dioxide, Stearic acid Magnesium stearate.

The hard capsule shells comprise of Gelatin, Purified Water, Titanium Dioxide, Sunset Yellow Fcf, Sodium Lauryl Sulfate, and Glycerin

Lactose Monohydrate, Lactose spray-dried and Gelatin are from bovine source.

【PACKAGE】

Aluminum foil and PVC 400/PVDC60 film in a form of blister with push-through foil.

60 capsules per 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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【PRODUCT REGISTRATION HOLDER】

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3791, Jalan Bukit Merah #09-20, E-Centre @ Redhill, Singapore 159471.

【DATE OF REVISION】

20210812