140mm

210mm

THALIMID 100mg Capsule

(Thalidomide)

تھیلیمڈ ۱۰۰ ملی گرام کیپسول

(تھیلیڈومائیڈ)

COMPOSITION:
Each capsule contains:
Thalidomide.....100mg
(USP Specifications)

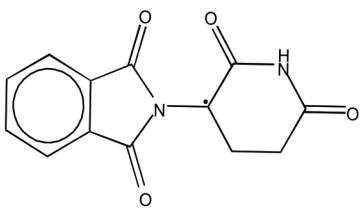
WARRNING: THALIDOMIDE SHOULD NEVER BE TAKEN BY PREGNANT WOMEN OR WOMEN CAPABLE OF BECOMING PREGNANT AS EVEN A SINGLE DOSE CAN CAUSE SEVERE BIRTH DEFECTS OR DEATH TO AN UNBORN BABY.

INDICATIONS AND USAGE :
Multiple Myeloma
THALIMID (Thalidomide) in combination with dexamethasone is indicated for the treatment of patients with newly diagnosed multiple myeloma (MM).
Erythema Nodosum Leprosum
THALIMID (Thalidomide) is indicated for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL).

THALIMID (Thalidomide) IS NOT INDICATED AS MONOTHERAPY FOR SUCH ENL TREATMENT IN THE PRESENCE OF MODERATE TO SEVERE NEURITIS.

THALIMID (Thalidomide) is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence.

DESCRIPTION:
THALIMID (Thalidomide), α-(N-phthalimido) glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide is C13H10N2O4 and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1.
Chemical Structure of Thalidomide



Note: = asymmetric carbon atom
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-(+). THALIMID (Thalidomide) is an equal mixture of the S-(-) and R-(+) forms and, therefore, has a net optical rotation of zero.
THALIMID (Thalidomide) is available as 100 mg capsule for oral administration. Active ingredient: Thalidomide.

CLINICAL PHARMACOLOGY :
Mechanism of Action
The mechanism of action of THALIMID (Thalidomide) is not fully understood. Cellular activities of thalidomide are mediated through its target cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex. THALIMID (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-) 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-in patients with erythema nodosum leprosum (ENL); however, it has also been shown to increase plasma TNF- 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 :
Absorption
Absorption of THALIMID (Thalidomide) is slow after oral administration. The maximum plasma concentrations are reached approximately 2-5 hours after administration. The absolute bioavailability of thalidomide from thalidomide capsules has not yet been characterized in human subjects due to its poor aqueous solubility.
Distribution
In human 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.

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Metabolism

In a 14C-radiolabel ADME study in humans, unchanged drug is the predominant circulating component. Thalidomide is not a substrate of the cytochrome P450 system. At therapeutic concentrations, thalidomide is not an inhibitor or inducer of human cytochrome P450 enzymes in vitro. Pharmacokinetic drug-drug interactions with substrates, inhibitors or inducers of CYP450 are not anticipated.

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 400 mg oral dose of radiolabeled 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 hours following dose administration. In humans, C-thalidomide is primarily excreted in urine (91.9% of the radioactive dose) mainly as hydrolytic metabolites while fecal excretion is minor (< 2% of the dose). Unchanged thalidomide is not eliminated by the kidney to a notable degree (<3.5% of the dose).

Effects of Weight

There is a linear relationship between body weight and estimated thalidomide clearance. In MM patients with body weight from 47-133 kg, thalidomide clearance ranged from approximately 6-12 L/h, representing an increase in thalidomide clearance of 0.605 L/h per 10 kg body weight increase.

Paediatric:No pharmacokinetic data are available in subjects below the age of 18 years.

DOSAGE AND ADMINISTRATION :

General Considerations

Drug prescribing to females of reproductive potential is contingent upon initial and continued negative results of pregnancy testing.

Consider dose reduction, delay, or discontinuation in patients who develop National Cancer Institute Common Toxicity Criteria (NCI CTC) Grade 3 or 4 adverse reactions and/or based on clinical judgment.

Multiple Myeloma

THALIMID (Thalidomide) is administered in combination with dexamethasone in 28-day treatment cycles. The dose of THALIMID (Thalidomide) is 200 mg administered orally once daily with water, preferably at bedtime and at least 1 hour after the evening meal. 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 adverse reactions such as constipation, somnolence, or peripheral neuropathy may benefit by either temporarily discontinuing the drug or continuing at a lower dose. With the abatement of these adverse reactions, the drug may be started at a lower dose or at the previous dose based on clinical judgment.

Erythema Nodosum Leprosum

For an episode of cutaneous ENL, THALIMID (Thalidomide) dosing should be initiated at 100 to 300 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after the evening meal. Patients weighing less than 50 kilograms should be started at the low end of the dose range.

In patients with a severe cutaneous ENL reaction, or in those who have previously required higher doses to control the reaction, THALIMID (Thalidomide) dosing may be initiated at higher doses up to 400 mg/day once daily at bedtime or in divided doses with water, at least 1 hour after meals.

CONTRAINDICATIONS:

Pregnancy

THALIMID (Thalidomide) can cause fetal harm when administered to a pregnant female. Thalidomide is contraindicated in females who are pregnant. Thalidomide is a powerful human teratogen, inducing a high frequency of severe and life-threatening birth defects, even after a single dose. Mortality at or shortly after birth has been reported in about 40% of infants. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential risk to a fetus. If pregnancy occurs during thalidomide treatment, the drug should be discontinued immediately.

Hypersensitivity

THALIMID (Thalidomide) is contraindicated in patients who have demonstrated hypersensitivity to the drug or its components.

WARNINGS AND PRECAUTIONS :

Embryo-Fetal Toxicity

Thalidomide is a powerful human teratogen that induces a high frequency of severe and life-threatening birth defects, even after a single dose. Mortality at or shortly after birth has been reported in about 40% of infants. When there is no satisfactory alternative treatment, females of reproductive potential may be treated with thalidomide provided adequate precautions are taken to avoid pregnancy.

Females of Reproductive Potential

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

Males

Thalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking THALIMID (Thalidomide) and for up to 4 weeks after discontinuing THALIMID (Thalidomide), even if they have undergone a successful

vasectomy. Male patients taking THALIMID (Thalidomide) must not donate sperm.

Blood Donation

Patients must not donate blood during treatment with THALIMID (Thalidomide) 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 THALIMID (Thalidomide).

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

Peripheral Neuropathy

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common (≥10%) and potentially severe adverse reaction of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months; however, peripheral neuropathy following relatively short-term use has been reported. The correlation with cumulative dose is unclear. Symptoms may occur sometime after thalidomide treatment has been stopped and may resolve slowly or not at all.

Dizziness and Orthostatic Hypotension

Patients should also be advised that thalidomide may cause dizziness and orthostatic hypotension and that, therefore, they should sit upright for a few minutes prior to standing up from a recumbent position.

Neutropenia

Decreased white blood cell counts, including neutropenia, have been reported in association with the clinical use of thalidomide. Treatment should not be initiated with an absolute neutrophil count (ANC) of <750/mm3. White blood cell count and differential should be monitored on an ongoing basis, especially in patients who may be more prone to neutropenia, such as patients who are HIV-seropositive. i

Thrombocytopenia, including Grade 3 or 4 occurrences, has been reported in association with the clinical use of thalidomide. Monitor blood counts, including platelet counts. Dose reduction, delay, or discontinuation may be required

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 log10 copies HIV RNA/mL, p = 0.04 compared to placebo). A similar trend was observed in a second, unpublished study conducted in patients who were HIV-seropositive

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. THALIMID (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 THALIMID (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 THALIMID (Thalidomide) in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Tumor Lysis Syndrome

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

Contraceptive Risks

Some contraceptive methods may pose a higher risk of adverse effects or may be medically contraindicated in some patients treated with THALIMID (Thalidomide). Because some patients may develop sudden, severe neutropenia and/or thrombocytopenia, use of an intrauterine device (IUD) or implantable contraception in these patients may carry an increased risk for infection or bleeding either at insertion, removal or during use..

Hypersensitivity

Hypersensitivity to THALIMID (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, THALIMID (Thalidomide) should be discontinued

Advers reactions:

The following adverse reaction are described in detail in other labeling section:

- Teratogenicity
- Venous and arterial
- Increased mortality in patients with MM when pembrolizumab is added to a thalidomide analogue and dexamethasone
- Drowsiness and somnolence
- Peripheral neuropathy
- Dizziness and orthostatic hypotension
- Neutropenia
- Thrombocytopenia
- Increased HIV viral load
- Bradycardia
- Stevens-Johnson syndrome and toxic epidermal necrolysis

- Seizures
- Tumor lysis syndrome
- Hypersensitivity

Paediatric Use

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

Renal Impairment

No clinical studies were conducted with THALIMID (Thalidomide) in patients with mild, moderate or severe renal function. Renal impairment is not expected to influence drug exposure since <3.5% of the dose is excreted in the urine as unchanged drug. 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 and blood samples for pharmacokinetics were collected at least 10 hours following the dose. Comparison of concentration-time profiles on a non- dialysis day and during dialysis showed that the mean total clearance increased by a 2.5-fold 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. In addition, there were no major differences in thalidomide PK between patients with end-stage renal disease and healthy volunteers. Thus, no dosage adjustment is needed for patients with renal impairment or patients on dialysis.

Hepatic Impairment

No clinical studies have been conducted in patients with hepatic impairment

Venous thromboemblism:

The use of THALIMID (Thalidomide) in multiple myeloma results in an increased risk of venous thromboembolism, such as deep venous thrombosis and pulmonary embolism. This risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial, the rate of venous thromboembolism was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% in patients receiving dexamethasone alone (p = 0.002). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Instruct patients to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Consider thromboprophylaxis based on an assessment of individual patients' underlying risk factors.

OVERDOSAGE :

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

HOW SUPPLIED:

10 capsules

STORAGE & INSTRUCTIONS:

Store between 20-25°C. Protect from heat, sunlight and moisture. Keep away from the reach of children.

To be sold on the prescription of a registered oncologist or on the demand from cancer hospitals and institutions only.

خوراک وطریقہ استعمال:

اونکولوجسٹ کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

دوا کو ۲۰-۲۵ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان رکھیں۔ دوا کو دھوپ، گرمی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔ صرف مستند اونکولوجسٹ یا کینسر ہسپتال کے نسخہ پر فروخت کریں۔

Manufactured by:

PHARMASOL

PRIVATE LIMITED

Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.