Package insert

Thado® Capsules (50 mg Thalidomide)

Warning

SEVERE, LIFE-THREATENING HUMAN BIRTH EFFECTS.

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 taken by a pregnant woman during her pregnancy can cause severe birth defects.

Before starting treatment, patients have read and signed the informed consent form for female/male patients for taking THADO® and are willing to comply with the constructions and will follow physicians' directions before taking thalidomide. Once treatment has started, if you are unable or unwilling to comply with the constructions or directions, you have to stop taking THADO® and inform your doctors.

For Prescribers

1. Major human fetal abnormalities related to thalidomide administration during pregnancy have been documented: Amelia (absent of limbs), phocomelia (short limbs), hypoplasticity of the bones, absent of bones, external ear abnormalities (including anotia, micro pinna, small or absent external auditory canals), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented. Mortality at shortly after birth has been repeated at about 40%.

2. Before prescribing, patients must read and sign the informed consent forms for female/male patients for thalidomide treatment. Only patients willing to comply with the constructions are qualified for thalidomide treatment.

3. Effective contraception must be used 1 month before beginning thalidomide therapy, during thalidomide therapy. Two reliable forms of contraception must be used simultaneously unless continuous unless due to hysterectomy or because the patient has been postmenopausal for at least 2 years. Women of childbearing potential should be referred to a qualified provider of contraceptive method.

Before starting treatment: women of childbearing potential should have a pregnancy test (sensitivity of at least 50 mIU/mL). The test should be performed within 24 hours prior to beginning therapy. A prescription for thalidomide for a woman of childbearing potential must

not be issued by the prescriber until a written report of a negative pregnancy test has been obtained by the presenter.

Once treatment has started: pregnancy test should occur weekly during the first month of use, then monthly thereafter in women with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every two weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding.

If pregnancy does occur during thalidomide treatment, thalidomide must be discontinued immediately. The patient must be reported immediately to _____ number at _____and also to TTY Biopharm Co., Ltd. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

For Female Patients

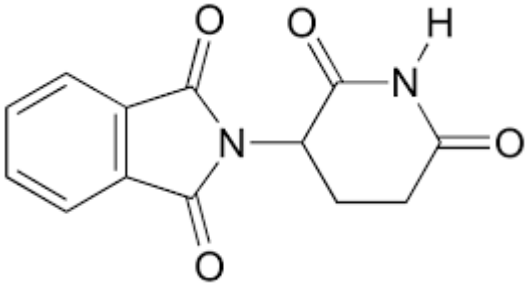
Thalidomide is contraindicated in WOMEN of childbearing potential. Female patients should sign the female consent form for THADO® and comply with the constructions in the female informed consent form for THADO® therapy before starting the treatment.

For Male Patients

Male patients should completely comply with the contents in and sign the male patient informed consent form for THADO® therapy before starting thalidomide treatment.

Description

Each THADO® capsule contains 50mg of active ingredient, thalidomide. 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. It is an off-white to white, nearly odorless, crystalline powder.



Mechanism of action

Thalidomide is an immunomodulatory agent with a spectrum of activity that is not fully characterized. There are many publishes for the studies in anti-inflammatory and anti-immunomodulatory, including inhibition for chemotaxis of neutrophil, decreasing the phagocytosis of monocyte, reducing the production of intermediates of oxygenation (superoxide and hydroxyl radicals), altering the ratio of T-cell (reducing helper T-cell and increasing suppressor T-cell), deducing IgM level and deducing the formation of IgM. Moreover, Administration of thalidomide has been reported to decrease circulating levels of Tumor Necrosis Factor-α (TNF-α) and Interferon-γ (INF-γ), relief the local and systemic symptoms and inhibiting the inflammatory cells in the lesion.

Indications

Treatment of Multiple Myeloma (MM) after failure of standard therapies.

Usage and administration

For prescription only.

THADO® must be only administered in compliance with all the instructions outlined in the informed consent form. Drugs prescribing to women of childbearing potential must be contingent upon initial and continued confirmed negative results of pregnancy testing. (Please refer to PRECAUTIONS)

Hepatocellular carcinoma and Multiple Myeloma (MM)

- THADO® should be intiated at 200 mg/day and not more than 800 mg/day, administered once daily with water, preferably at bedtime and at least 1 hour after evening meal.
- Patients should not take double doses of THADO® in one time, when patients miss one dose of THADO®, patients should make up as soon as possible but the timing of dose making up should not be close to the next dose.

Pharmocokinetics

Absorption:

From the other thalidomide products, the mean time to peak plasma concentrations (T_{max}) is 2.9 to 5.7 hours indicating 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 (see Table 1 below). 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 of absorption.

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

Population/Single Dose	AUC (μg-hr/mL)	Cmax (μg/mL)	Tmax (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%)

Co-administration 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.

Distribution:

It is not clear whether thalidomide is distributed in the semen.

Metabolism:

At the present time, the exact metabolic route and the fate of thalidomide is not known. Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple metabolites. 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 100 mg/day, thalidomide does not induce or inhibit its own metabolism.

Elimination:

As indicated in Table 1, 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 elimination of thalidomide in humans is not known 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 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 and in increased peak plasma levels (see Table 1).

Patients with Renal Insufficiency and/or Hepatic Disease: The pharmacokinetics of thalidomide is patients with renal dysfunction and/or hepatic impairment has not been determined.

Age: Analysis of the data from pharmacokinetic studies ranging in age from 20 to 69 years does not reveal any age-related changes.

Pediatric: No pharmacokinetic studies in subjects below the age of 18 years.

Overdosage

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

Drug abuse and dependence

Physical and psychological dependence has not been reported in patients taking thalidomide. However, as with other tranquilizers/hypnotics, thalidomide too has been reported to create in patients habituation to its soporific effects.

Adverse reactions

Thalidomide is associated with drowsiness/somnolence, peripheral neuropathy, dizziness/orthostatic hypotension, neutropenia, and HIV viral load increase. Hypersensitivity to thalidomide and bradycardia in patients treated with thalidomide has been reported. Somnolence, dizziness, and rash are the most commonly observed adverse events associated with the use of thalidomide. The incidences of adverse event profiles from these uses are summarized in Table 2. All adverse events were mild to moderate in severity, and none resulted in discontinuation.

Table 2: Incidence of adverse event in thalidomide-controlled clinical trials

Adverse event	AEs (ENL Patients)	AEs (HIV-seropositive Patients)	
		Thalidomide	Placebo

Body system	50 – 300 mg/day (N = 24)	100 mg/day (N = 36)	200 mg/day (N = 32)	(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 multiple 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%)
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%)

Hemauria	0	4 (11.1%)	0	1 (2.9%)
Impotence	2 (8.3%)	1 (2.8%)	0	0

Warnings

1. The most serious toxicity associated with thalidomide is its documented human teratogenicity, including phocomelia and death to the fetus. If pregnant women take the drug in 35 to 50 days after last menstrual period, even one single dose could cause severe birth defects.
2. Thalidomide is common to cause peripheral neuropathy. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following relatively short-term use also exist. Symptoms include numbness of toes and feet, tingling or pain in the hands and feet, symmetrical sensorimotor neuropathy, slightly orthostatic tremor uncontrolled ankle cramps, nails crumbly and red palm. Stop therapy with mild symptom appearance and then patients will completely recover soon. If continue therapy with symptom appearance, numbness will become permanent and expand to legs. The possible mechanism of peripheral neuropathy may be the degeneration of neuroxon and sensory nerve fibers of legs will be first affected.
3. The drug is harmful thus patient must use under physician order.

Precautions

1. Pregnancy category: X (Pregnant women are restricted to use)
2. THADO® is not used to patients hypersensitive to thalidomide. Signs and symptoms include erythematous macular rash, possibly associated with fever, tachycardia and hypotension. If severe, may necessitate interruption of therapy. If the reaction recurs when dosing is resumed, THADO® should be discontinued.
3. Bradycardia in association with thalidomide use has been reported. At present there have been no reports of bradycardia requiring medical or other intervention.
4. Before dispensing, patients must read and sign the female/male inform consent form for THADO® therapy. Only patients are willing to comply with the instructions in the inform consent form are allowed to be prescribed THADO® (thalidomide).
5. Thalidomide is contraindicated in pregnant women, women capable becoming pregnant and nursing mothers. Women may become pregnant are required at least two types of contraception 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 1 month prior to initiating treatment with thalidomide, during therapy with thalidomide, and continuing for 1 month discontinuation of thalidomide therapy.

6. Males receiving thalidomide must always use a latex condom during any sexual contact with women of childbearing potential during thalidomide therapy and 1 month discontinuation of Thalidomide therapy.
7. Women of childbearing potential should have a pregnancy test performed (sensitivity of at least 50 mIU/mL). The test should be performed within 24 hours prior to beginning therapy and the weekly during the first 4 weeks of Thalidomide therapy, then monthly 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.
8. Thalidomide frequently causes drowsiness and somnolence. Patients should be instructed to avoid driving a car or operating machinery.
9. Thalidomide may cause dizziness and orthostatic hypotension. Therefore, patients should be advised to sit upright for a few minutes prior to standing up from a recumbent position.
10. Thalidomide therapy 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. If AND 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.
11. 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. Consideration should be given to electrophysiological testing, consisting of measurement of sensory nerve action potential (SNAP) amplitudes at baselines 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 limit further damage, if clinical appropriate. Usually, treatment with thalidomide should only be reinitiated if the neuropathy returns to baseline status.
12. Increased HIV-viral load: it has been reported that in an HIV-seropositive patient population, plasma HIV RNA levels were found to increase. The clinical significance of this increase is unknown. 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.
13. Drug interactions: it has been reported to enhance the sedative activity of barbiturates, alcohol. Chlorpromazine and reserpine. Medications known to be associated peripheral neuropathy should be used with caution in patients receiving thalidomide.
14. Concomitant use of HIV-protease inhibitors, griseofulvin, rifampicin, rifabutin, phenytoin, or carbamazepine with hormonal contraceptive agents, may reduce the effectiveness of the contraception. 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 reproductive heterosexual sexual intercourse.

15. THADO® should be prescribed only for the patient and must not be shared with anyone.
16. THADO® must be kept out of the reach of children.

Contraindications

Hypersensitivity to thalidomide.

Nursing mothers, pregnant women and women of childbearing potential.

Potency Each capsule contains 50mg thalidomide

Package Each blister pack contains 10 capsules and put into the paper box. Each box contains 1, 2, 3, 4, 5 or 6 blisters.

Storage This drug must be kept in tight container and avoid heat and moisture and light exposure. Store below 30°C. Please keep out of the reach of children.

Expiration See label on carton.

References

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