Zuvimide

Thalidomide Capsules USP

WARNING: 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.

PLEASE REFER TO PATIENT INFORMATION SHEET FOR DETAILED INSTRUCTIONS FOR PATIENTS.

COMPOSITON:

Zuvimide -100

Each Capsule contains:

Thalidomide USP..... 100 mg.

Zuvimide -50

Each Capsule contains:

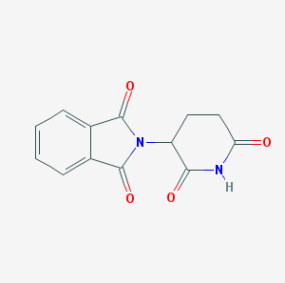
Thalidomide USP..... ..50 mg.

DESCRIPTION

Thalidomide is an immunomodulatory agent with a promising activity against a variety of tumors and cutaneous manifestations of Erythema Nodosum Leprosum (ENL). Thalidomide is an off-white to white, nearly 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 - (+) Thaildomide is an equal mixture of the S-(-) forms and R-(+) forms and, therefore, has a net optical rotation of zero.

CHEMISTRY

Thalidomide is a (N-phthalimido) glutarimide. The empirical formula for thalidomide is C13H10N2O4 and the gram molecular weight is 258.2. Chemical Structure Of Thalidomide



PHARMACOLOGY

Mechanism of action

Thalidomide possesses immunomodulatory properties but the exact mechanism of its action is not fully understood yet. Thalidomide supresses the excessive production of Tumor Necrosis Factor - alpha (TNF-a) by accelerating the degradation of mRNA encoding the protein 1.4. The antiangiogenic effects of thalidomide may be attributed to its ability to cause oxidative damage to DNA mediated by free radicals and by inhibiting vascular endothelial growth factor and basic fibroblast growth factor -2 which are mainly involved in angiogenesis.

Pharmacokinetics

Following oral administration of thalidomide, the mean time to peak plasma concentrations (Tmax) ranges from 2.9 to 5.7 hours indicating that it is slowly absorbed from the gastrointestinal tract, while the extent of absorption (as measured by area under the curve [AUC]) is proportional to dose but the peak concentration (Cmax) does not increase in a proportional manner

Pharmacokinetic Parameter values (Mean (%CV) for Thalidomide following single dose:

Population/ Single Dose	AUC O-X (mg.h/ml)	Cmax (mg./ml)	Tmax (hrs)	(Half-life) (hrs)
Healthy Subject (n=14)				
50 mg 200 mg 400 mg	4.9 (16%) 18.9 (17%) 36.4 (26%)	0.62 (52%) 1.76 (30%) 2.82 (28%)	2.9 (66%) 3.5 (57%) 4.3 (37%)	5.52 (37%) 5.53 (25%) 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%)

CV= covariance; AUC = area under the plasma concentration - time curve; Cmax= maximum plasma concentration;

Tmax= time to maximum plasma concentration.

The mean plasma protein binding for (+) -R and (-) - (S)- thalidomide is 55% and 66% respectively. The exact metabolic route and fate of thalidomide is presently unknown in humans. Thalidomide itself does not appear to be metabolized in liver to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple metabolities. The mean half-life of elimination ranges from approximately 5 to 7 hours following a single dose and is unchanged upon multiple dosing. Thalidomide has a renal clearance or 1.15 ml/ minute with less than 0.7% of the dose excreted in the urine as unchanged drug. No pharmacokinetic studies have been conducted in subjects with renal or hepatic dysfunction or patients below the age of 18 years.

CLINICAL STUDIES:

Two double blind randomized, controlled trials reported the dermatologic response to a 7 day course of 100 mg thalidomide (four times daily) or control.

Double Blind, Controlled Clinical Trails of Thalidomide in Patients with ENL: Cutanaous Response.

Reference	No. of Patients	No. Treatment Courses	PERCENT RESPONDING	
Lyer et at 5 Bull W.H.O. 1971; 45: 719	92	204	Thalidomide 75%	Asprin 25%
Sheskin et al6 In J Lep 1969; 37:135	52	173	Thalidomide 66%	Placeto 10%

Various studies indicate the potential of thalidomide in early and relapsed multiple myeloma. The overall survival rates of 60 percent and two year event free rate of 15 percent were reported in a follow up of a phase II trial of patients with advanced and refractory multiple myeloma when treated with thalidomide as a single agent 7. In an another study enrolling 84 chemotherapy - refractory multiple myeloma patients, thalidomide was able to induce a marked and durable response in about one third of the patients. At 12 months follow - up, 22% and 58% of patients were event free and alive, respectively5.

Thalidomide regimen dosing generally ranged from 200 mg (initial dose) to a maximum of 800 mg daily, with partial response usually characterized by reduction of 50% or more in serum myeloma (M) protein. Remission durations ranged from 2 months to more than a year.

INDICATIONS

* For acute treatment of the cutaneous manifestations of moderate to severe Erythma Nodosum Leprosum (ENL) and for the treatment of multiple myeloma.

Dosage and Administration

Drug prescribing to women of child bearing potential should be contingent upon initial and continued conformed negative results of pregnancy testing.

* FOR ENL:

Thalidomide dosing should be started at 100 to 300 mg / day for cutaneous ENL. Dosing with thalidomide should usually continue until signs and symptoms of active reaction have subsided, usually a period at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks .

For Multiple Myeloma

WARNING

* Drowsiness and somnolence:

Thalidomide use has been reported to induce drowsiness and somnolence and somnolence patients should be advised to avoid hazardous tasks and taking other medications that may cause drowsiness.

* Peripheral neuropathy:

Thalidomide has the potential to cause peripheral neuropathy that may be irreversible. Patients should be examined at regular intervals during thalidomide therapy to detect early signs of neuropathy. If symptoms of drug - induced neuropathy develop, thalidomide should be discontinued after appropriate clinical evaluation.

* Orthostatic hypotension and dizziness:

Thalidomide may cause dizziness and orthostatic hypotension, therefore, the patient should be advised to sit upright for a few minutes prior to standing up from a recumbent position.

* Hypersensitivity :

The occurrence of erythematous muscular rash associated with fever, tachycardia, and hypotension have been reported with thalidomide. Thalidomide should be discontinued if the reaction recurs upon resuming the dose.

* Bradycardia:

Bradycardia has been observed in some thalidomide-treated patients but its clinical significance is presently unknown.

* Stevens Johnson Syndrome and Toxic Epidermal Necrolysis: Serious dermatologic reactions have been reported with thalidomide. The treatment should be discontinued if a skin rash occurs and only resumed following appropriate clinical evaluation.

* Seizures:

Seizures have been reported in some patients receiving thalidomide. Patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely during thalidomide therapy for clinical changes that could precipitate acute seizure activity.

PRECAUTIONS

* Birth Defects

Thalidomide can cause potentially severe birth defects. So, patients should be instructed to take adequate precautions to avoid pregnancy (See patient information leaflet).

* Neutropenia:

Neutropenia has been observed with the use of thalidomide. Treatment with thalidomide should not be initiated with an absolute neutrophil count (ANC) of <750 /mm. Total & differential white blood cell count should be monitored on an ongoing basis.

ADVERSE REACTIONS :-

The main adverse effects associated with the use of thalidomide are:

* 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 (ranging from 35 to 50 days after the last menstrual period). Anomalies of limbs, eyes, heart, kidneys, external ears, CNS, genitourinary tract and esophageal or duodenal atresia have been reported with thalidomide exposure.

* Peripheral Neuropathy :

Peripheral neuropathy is a commonly occuring (10-50%), potential side effect asoociated with the use thalidomide. It generally occurs following chronic use over a period of months and is characterized as a distal anonopathy with the long and large diameter motor and sensory axons of the feet and hands being affected. Degeneration gradually moves proximally (dying back) towards the nerve cell body. There is a superficial sensory loss in the feet and hands. The clinical symptoms includes symmetric sensorimotor neuropathy, painful paresthesias in the hands and feet, distal hypoesthesia, proximal weakness in the.

ower limbs, slight postural tremor, leg cramps, absent ankle jerks, brittle nails and redness of the palms. Older patients (>60 years) are reported to be more susceptible to thalidomide- associated neuropathy than younger patients.

* Sedation:

Somnolence and dizziness occur more frequently at doses of 200 to 400 mg than at lower doses. In patients infected with HIV, drowsiness, dizziness and mood changes occurred in 33% to 100% of patients. In various trials in patients with ENL the incidence of somnolence was reported to be 37.5% 9 . Administering thalidomide in the evening can minimize drowsiness. For patients who require higher doses, the dose can be increased by 100 to 200 mg/d every 4 to 7 days. Tolerance to the sedative effects usually occurs overtime.

* Gastrointestinal toxicity :

Constipation has been reported in 3% 30% of patients. Other gastrointestinal effects observed with thalidomide therapy are nausea, vomiting and dry mouth 10.

* Dermatological toxicity

Dry skin, alopecia, pruritus, erythematous and papulovesicular eruptions have been reported in about 10% of patients. The incidence of rash appears to vary depending on the treatment population. Rash has been reported in patients with chronic graftversus -host diseas (GVHD; 20%, 16/80); cancers; prurigo nodularis; and HIV aphthous ulcers (24%, 7/29) treated with thalidomide. Eosinophilia in association with rash also has been reported 11.

* Neutropenia :

Decreased white blood cell (WBC) counts including neutropenia, have been reported in association with the clinical use of thalidomide. The incidence is usually less than 1 % but it may be higher in patients with HIV.

Drug Interactions

Thalidomide potentiates the sedative activity of barbiturates, alcohol, chlorpromazine and reserpine.

* Carcinogenesis, Mutagenesis, Impairment of Fertility

There is no evidence of mutagenic effects of thalidomide. No animals studies to characterize the effects of thalidomide on fertility have been conducted. Long-term carcinogencity tests have not been conducted using thalidomide,

Overdose

There have been no reported fatalities in doses of up to 14.4 grams 12.

For the treatment of multiple myeloma the dose range used is 200-800 mg dialy.

CONTRAINDICATIONS

* Patients with known hypersensitivity to thalidomide.

Pregnancy: Category X

* Thalidomide is contraindicated in pregnant women and women of child bearing potential who are not using two forms of contraception.

USE IN NURSING MOTHERS

* It is unknown whether thalidomide is excreted in human milk. However, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into acount the risks and the benefits.

Storage: Store below 25°C, protected from light & moisture.

PRESENTATION

Zuvimide -100 : Strip of 10 Capsule (Pack of 3x10's)

Zuvimide -50 : Strip of 10 Capsules (Pack of 3x10's)

Manufactured in India by:

ZUVIUS LIFESCIENCES PVT. LTD.
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