Drug Monograph

A - Drug Name

thalidomide

COMMON TRADE NAME(S): Thalomid®

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B - Mechanism of Action and Pharmacokinetics

Thalidomide is an immunomodulatory agent with anti-inflammatory activity. The drug also has anti-angiogenic, sedative and hypnotic effects. The mechanisms of action of the immunomodulatory and anti-inflammatory effects of thalidomide are complex and have not been fully determined, but thalidomide appears to reduce TNF-α production, modulate integrins, alter T-cell ratios or T cell-derived cytokines and modulate interleukin production.

Thalidomide was developed in 1956 as an oral sedative, but was withdrawn from the market in 1961 because of its teratogenic effects. The mechanism for its teratogenicity remains unknown, but may be associated with anti-angiogenic properties.

Absorption	Oral: Poorly soluble and slowly absorbed. Absorption appears to be saturable. High fat meals delay the time to peak concentration, but do not appear to substantially affect the extent of absorption of thalidomide.
Distribution	Thalidomide is a nonpolar compound and it appears to be distributed throughout the body. Crosses the placenta and found in semen. Cross blood brain barrier? yes PPB 55 - 66 %
Metabolism	The exact metabolic fate of thalidomide in human is unknown. Hepatic metabolism of thalidomide is limited. The principal metabolic pathway of thalidomide appears to be non-enzymatic spontaneous hydrolysis. Does not appear to be a substrate, inhibitor or inducer of CYP 450. Thalidomide does

	not induce or inhibit its own metabolism.	
	Active metabolites	No
	Inactive metabolites	Yes (most likely)
Elimination	Urine	92% of the dose (mainly as hydrolytic metabolites), 0.7% as unchanged drug
	Half-life	5 - 7 hours

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C - Indications and Status

Health Canada Approvals:

- In combination with melphalan and prednisone for treating previously untreated multiple myeloma in patients 65 years and older.

Thalidomide is only available through a controlled distribution program- RevAid®. For more information, please call 1-888-revaid1 (1-888-738-2431) or visit www.revaid.ca

Other Uses:

- In combination with dexamethasone for newly diagnosed multiple myeloma for patients who are candidates for stem cell transplant
- Maintenance therapy post stem cell transplant
- Relapsed refractory myeloma

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

Thalidomide is usually used in combination with melphalan and prednisone. Adverse effects noted below (unless indicated) are from controlled clinical trials of combination, where the incidence in the thalidomide combination arm was considered higher and clinically relevant (in general incidence

≥10% higher or severe event incidence ≥ 2%). Life-threatening adverse events reported from post-marketing surveillance are also indicated.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (rare)	E
	Arterial thromboembolism (rare)	E
	Cardiotoxicity (rare)	L
	Hypotension (<10%)	I
	Venous thromboembolism (10%)	E
Dermatological	Rash (<10%) (may be severe)	E
Gastrointestinal	Abdominal pain (<10%)	E
	Constipation (23%)	E
	Diarrhea (<10%)	E
	Dry mouth (<10%)	E
	GI obstruction / perforation (rare)	E
	Nausea, vomiting (<10%)	E
General	Edema (<10%)	E
	Fatigue (<10%)	E
Hematological	Myelosuppression ± infection, bleeding (44%) (severe)	E
Hepatobiliary	Hepatic failure (rare)	D
	↑ LFTs (rare, may be severe)	E
	Pancreatitis (rare)	E
Hypersensitivity	Hypersensitivity (rare)	I
Infection	Infection (<10%) (may be severe, including opportunistic)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (K - < 10%)	E
Musculoskeletal	Musculoskeletal pain (<10%)	E
Neoplastic	Leukemia (secondary) , MDS (rare; up to 4% with MPT after 3 years)	L
Nervous System	Confusion (>10%)	E
	Depression (<10%)	E
	Dizziness (12%)	I
	Neuropathy (19%) (peripheral and autonomic)	E D
	Seizure (rare)	E
	Somnolence (23%)	E

	Tremor (11%)	E
Renal	Renal failure (<10%)	D
Respiratory	Cough, dyspnea (<10%)	E
	Pneumonitis (<10%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for thalidomide include myelosuppression ± infection, bleeding, constipation, somnolence, peripheral neuropathy, dizziness, tremor, abdominal pain, confusion, cough, dyspnea and depression.

The **sedative properties** of thalidomide are believed to be due to activation of the thalamic and hypothalamic sleep centres and are dose-related, and are additive with other sedatives. Administering thalidomide at bedtime minimizes daytime somnolence, but patients should still be cautioned to avoid situations in which drowsiness could be hazardous. It may be necessary to adjust concomitant sedative medications.

The mechanism by which thalidomide-associated **edema** occurs is unknown, but is mild and short-lived. Dose modification is usually not necessary.

The most common **rash** described in association with thalidomide use is a pruritic, erythematous, macular rash over the trunk, back and proximal extremities, which does not appear to be dose-related, and occurs 10 to 14 days after starting therapy. The rash usually resolves within 24 hours after discontinuation. Serious dermatological reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, which may be fatal, have rarely been reported in association with thalidomide therapy; patients should not be re-challenged. Hypersensitivity reactions (i.e. rash, fever, tachycardia, hypotension, etc) have also been reported.

Cases of **viral reactivation** have been reported, including hepatitis B and C virus (HBV, HCV) infections and may result in acute hepatic failure, including fatal events. Use with caution in patients previously infected with HBV or HCV.

Thalidomide-associated **peripheral and autonomic neuropathies** are not dose-related and are associated with axonal degeneration without demyelination. Baseline evaluation and monitoring should be considered in patients at risk. Neuropathy may be irreversible if thalidomide is not discontinued early, or may develop after treatment is discontinued.

Dizziness and hypotension may be related to the central sedative action of thalidomide. Administering thalidomide at bedtime may minimize symptoms due to decrease in blood pressure, but patients should still be cautioned to sit upright for several minutes before standing up from a recumbent position.

Bradycardia and AV block have been reported.

Venous and arterial thromboembolism are increased especially in combination with chemotherapy and/or steroids, or in high risk patients (age≥ 65 years, male patients, hyperlipidemia, hypertension, diabetes, obesity, renal disease and tobacco use); patients should be closely monitored and prophylaxis considered, especially for the first 5 months of treatment.

Severe bleeding (especially when used with other drugs that may increase the risk of bleeding) or **infection** have been reported in patients using thalidomide with melphalan and prednisone. Increased viral loads have been reported when thalidomide is used in HIV seropositive patients.

Thalidomide was withdrawn from the worldwide market in 1961 because of its **teratogenic** and neurotoxic effects. Severe congenital malformation or fetal deaths are associated with maternal thalidomide usage. Thalidomide is detected in sperm and seminal fluid. Both male and female patients must adhere to the requirements of the RevAid program. (Refer to section G.)

Hepatotoxicity has been reported and may be fatal. The pattern may be hepatocellular or cholestatic, usually occurred within the first 2 months of therapy and resolved spontaneously without treatment after discontinuing thalidomide.

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E - Dosing

Refer to protocol by which patient is being treated. Prophylactic anticoagulants should be used, especially in patients with other risk factors and for at least the first five months of treatment. Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Thalidomide may only be prescribed and dispensed by physicians and pharmacists registered with RevAid®. Patients must also be registered and meet all conditions of the RevAid® program. Call 1-888-RevAid1 or log onto www.RevAid.ca. Also refer to section G.

Adults:

Patients ≤ 75 years: 200 mg PO daily

Patients > 75 years: 100 mg PO daily

Refer to the MPT regimen monograph for details when given with melphalan and prednisone.

Dosage with Toxicity:

Dose levels (thalidomide):

Dose level	Age ≤ 75 years	Age > 75 years
0	200 mg daily	100 mg daily
-1	100 mg daily	50 mg daily
-2	50 mg daily	50 mg every other day
-3	50 mg every other day	Discontinue

Toxicity	Thalidomide Dose and Action	Melphalan/Prednisone Dose and Action (if applicable)
ANC < 1.5 (x 10^9/L)	No change	Refer to the MPT regimen, dosage with toxicity section.
Grade 3 or 4 thromboembolism	Hold, ensure adequately anticoagulated. Maintain dose level unless occurred despite adequate anticoagulation; if so, discontinue	No change
Grade 3 neurotoxicity	Hold until resolves to ≤ grade 1, then decrease by 1 dose level	No change
Grade 4 neurotoxicity	Discontinue	Discontinue
Grade 3 rash or mild hypersensitivity	Hold until rash resolves to ≤ grade 1, then decrease by 1 dose level	No change
Grade 4 rash or severe hypersensitivity	Discontinue	Discontinue
Grade 3 or 4 constipation	Initiate bowel regimen and hold until resolves to ≤ grade 2, then decrease by 1 dose level	No change

Over sedation	Consider short drug holiday or ↓ dose; may restart at the same or lower dose when recovered	No change
Severe syncope/bradycardia	Consider ↓ dose or discontinue	No change
Other grade 3 toxicity	If thalidomide-related, hold until resolves to ≤ grade 2 then decrease by 1 dose level	No change
Other grade 4 toxicity	Discontinue	

Dosage with Hepatic Impairment:

Not specifically studied in patients with hepatic impairment.

Dosage with Renal Impairment:

Not specifically studied in patients with renal impairment. Monitor patients with severe renal impairment as metabolites are eliminated via urine. Some data suggested that no dose modification is needed in renal impairment (including patients on dialysis); however monitor closely as there have been reports of fatal hyperkalemia in renally impaired patients.

Dosage in the elderly:

For patients older than 75, the recommended starting dose is 100 mg/day. The frequency of serious adverse effects, such as atrial fibrillation, back pain and fall, including fatal reactions was higher in patients over 75 compared to younger patients.

Children:

Not recommended for use in patients under 19 years of age.

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F - Administration Guidelines

- Oral self-administration; taken on a specified schedule (usually once daily) once daily preferably with a glass of water, with or without food at about the same time each day.
- Swallow capsules whole; they should not be broken, chewed, or opened.
- Thalidomide should be administered at bedtime to minimize adverse effects such as dizziness and somnolence.
- Avoid use of alcohol since this may potentiate sedation.
- Do not extensively handle the capsules. Females who may become or plan to become pregnant can handle thalidomide if they are using latex gloves.
- Remove capsule from the original packaging only at administration time. Do not put the capsule on the counter or dish/container before taking it; give the capsule directly from the packaging and place into the mouth.
- If a dose is missed, take it if it is within 12 hours from the missed dose, otherwise skip this and give the next dose as scheduled. Do not double the dose to make up for the forgotten one.
- Drug available by outpatient prescription in pharmacy registered with the RevAid® program. Please call 1-888-RevAid-1 or log onto www.RevAid.ca (see section G)

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G - Special Precautions

Contraindications:

- Patients with peripheral neuropathy, or with known hypersensitivity to thalidomide, lenalidomide, or pomalidomide.
- Women who are pregnant.
- Breastfeeding women.
- Patients unable to follow or comply with the required contraceptive measures (see below section regarding the RevAid® program).

Other Warnings/Precautions:

- Patients should be warned of the risk of drowsiness, dizziness or orthostatic hypotension. Caution in patients using sedatives or alcohol.
- May increase viral load if used in patients with HIV.
- Use with caution and monitor closely in patients with previous viral infections such as HBV and HCV.
- Use with caution in patients with risk factors for VTE or ATE, or using thrombogenic agents. Oral contraceptives should be avoided due to the increased risk of VTE.

- Use with caution in combination with corticosteroids in myeloma due to the risk of thromboembolism - consider prophylactic anticoagulation.
- Use with caution in patients with risk factors for peripheral neuropathy, taking neurotoxic drugs, or taking drugs that may cause severe skin reactions.

Pregnancy and Lactation:

Although in vitro or animal studies suggested thalidomide to be non-mutagenic, non-genotoxic and non-carcinogenic, it is associated with **secondary malignancies**; fertility may be affected. Thalidomide is excreted into milk in animals; **breastfeeding is contraindicated**. It is a known human **teratogen**, is **fetotoxic**, an **abortifacient**, and can cause severe, life-threatening birth defects or fetal death if taken during pregnancy, especially 34-50 days after the beginning of the last menstrual period. The drug can cause teratogenic effects even if only a single dose of the drug is taken during pregnancy. Thalidomide is **contraindicated in pregnant women and in females of childbearing potential and in males who do not comply with the contraception conditions of the RevAid® program**.

Thalidomide is present in the semen, and there is a potential risk of birth defects, stillbirths and spontaneous abortions if fetal exposure occurs through the semen of male patients.

Only physicians registered with RevAid may prescribe the drug. RevAid is a controlled distribution program run by Celgene through registered RevAid pharmacies for Revlimid® and Thalomid®. All patients must comply with the requirements of the RevAid program. REFER TO FULL DETAILS ON THE REVAID® PROGRAM.

Male patients:

- Must be capable of understanding and complying with the patient registration, education, and safety requirements of the RevAid®,
- Mandatory contraceptive measures for men (condoms should be used even with vasectomized males).
- Should not donate semen while taking thalidomide and for 4 weeks after treatment cessation.
- Must inform their female sexual partners of child-bearing potential that he is taking thalidomide, of the potential risk of birth defects, stillbirths, and spontaneous abortions, and that a condom must be used during any sexual contact.
- If a pregnancy occurs in a partner of a male patient taking thalidomide, the female partner should be referred to a physician specialized in teratology for evaluation and advice.

Females of childbearing potential (all women except those who had hysterectomy or bilateral oophorectomy):

- Must be capable of understanding and complying with the patient registration, education, and safety requirements of the RevAid® program,
- Undergo regular pregnancy testing
- Use two simultaneous contraception methods (must be started at least one month prior to starting treatment, continued during dose interruptions, during treatment and for at least 1 month following the cessation of thalidomide).
- It is not recommended for patients to use hormonal contraceptives due to the increased risk of thromboembolism.
- If pregnancy occurs during treatment, thalidomide must be discontinued and patient referred to

a gynecologist/obstetrician for evaluation and counselling.

Patients should not donate blood while taking thalidomide and for 4 weeks after stopping therapy to prevent fetal exposure via transfusion of pregnant women.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Neurotoxins (i.e. lithium, vincristine, cisplatin, bortezomib)	↑ neuropathy	Additive effects	Caution
Sedatives (i.e. barbiturates, alcohol, chlorpromazine)	Enhance CNS sedation	Additive	Caution
Beta-blockers, anticholinesterase agents	↑ risk of bradycardia	Additive effects	Caution
Hormonal therapy (contraception/HRT), erythropoietic agents, corticosteroids	↑ risk of thromboembolic events	Additive	Caution; monitor carefully; consider prophylaxis with anticoagulants

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and monthly
RevAid requirements regarding pregnancy tests for women of childbearing potential	Before starting and as indicated per RevAid
Neurological exams	Baseline and monthly for the first 3

	months, and periodically thereafter; consider using electrophysiologic testing at baseline and every 6 months.
Liver function tests	Baseline and periodic, especially in patients with pre-existing liver disorder or with concurrent use of potentially hepatotoxic medications
EKG	as clinically indicated (bradycardia, AV block)
Hepatitis serology	If hepatitis or reactivation suspected
Clinical assessments of bleeding, rash, constipation, CNS effects (including neuropathy, seizures, somnolence), arterial and venous thromboembolism, syncope/bradycardia, infections, hepatitis	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Renal function tests	Baseline and regular
Seizures	as clinically indicated, especially in at risk patients
HIV viral load (in HIV-seropositive patients)	After the first and third months of treatment, and then every 3 months

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- thalidomide - Multiple myeloma in patients ≥65 years of age in combination with melphalan and prednisone, with specific criteria

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K - References

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June 2019 Updated emetic risk category.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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