

**DRUG NAME: Thalidomide****SYNONYM(S):****COMMON TRADE NAME(S):** THALOMID®**CLASSIFICATION:** miscellaneous

*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.*

**MECHANISM OF ACTION:**

The mechanism of action of thalidomide is not completely understood. *In vitro* and *in vivo* studies indicate that it inhibits the production of tumor necrosis factor-alpha in monocytes. Thalidomide may induce the down-regulation of integrin receptors and other surface adhesion proteins, reduce IgM production, alter CD4/CD8 T-cell ratios as well as increase the total numbers of CD8 and CD4 T-cells,<sup>1</sup> and inhibit angiogenesis. Anti-inflammatory properties have been suggested through decreasing the production of oxygen-free radicals and other mediators in inflammatory response.<sup>2,3</sup> Thalidomide may enhance cell-mediated immunity by directly stimulating cytotoxic T-cells.<sup>4,5</sup>

**PHARMACOKINETICS:**

Interpatient variability	significant interpatient variability especially in absorption and half-life <sup>6</sup>	
Oral Absorption	high fat meals increase the time to peak concentration but results in < 10% change in AUC or peak plasma concentration <sup>3,6</sup>	
	time to peak plasma concentration	2.5-4.4 h <sup>3,6</sup> (6 h with high fat meal)
Distribution	mostly in GI tract, liver, kidneys (less in muscle, brain, adipose tissue); <sup>3</sup> present in ejaculate <sup>7</sup>	
	cross blood brain barrier?	yes
	volume of distribution	121 L (70-83 L in HIV patients) <sup>3,6</sup>
	plasma protein binding	moderately bound to plasma proteins (55-66%) <sup>3,6</sup>
Metabolism	exact metabolism not known, possibly by non-enzymatic spontaneous hydrolysis in plasma <sup>3,6</sup>	
	active metabolite(s)	none
	inactive metabolite(s)	phthalic acid
Excretion	not well defined	
	urine	0.7% excreted unchanged <sup>3,6</sup>
	feces	no information found
	terminal half life	3-7 h (more variable in HIV patients) <sup>3,6</sup>
	clearance	170-207 mL/min <sup>6</sup>
Elderly	no clinically significant difference	
Children	no clinically significant difference	

Adapted from reference<sup>3</sup> unless specified otherwise.

**USES:****Primary uses:**

Multiple myeloma<sup>8-19</sup>

**Other uses:**

Graft versus host disease<sup>20-33</sup>  
 Melanoma<sup>34-36</sup>  
 Myelodysplastic syndrome<sup>37,38</sup>  
 Prostate cancer<sup>39</sup>  
 Renal cell carcinoma<sup>36</sup>

\*Health Canada Therapeutic Products Programme approved indication

**SPECIAL PRECAUTIONS:****Contraindicated:**

- in pregnant women<sup>40</sup>
- in women with childbearing potential or sexually mature males except as provided through the controlled distribution program RevAid®<sup>40</sup>
- relatively contraindicated in the presence of neutropenia or peripheral neuropathy.<sup>3,41</sup>

**Carcinogenicity:** Second primary malignancies, in particular acute myeloid leukemia and myelodysplastic syndrome, have been observed in the post market setting.<sup>40,42</sup>

**Mutagenicity:** Not mutagenic in Ames test or mammalian *in vitro* mutation test. Thalidomide is not clastogenic in mammalian *in vitro* or *in vivo* chromosome tests.<sup>3</sup>

**Fertility:** no information found.

**Pregnancy:** FDA Pregnancy Category X. Thalidomide is teratogenic in humans. Birth defects are believed to occur if embryo is exposed to even a single dose from day 21-56 after conception. Malformations include amelia and phocomelia, polydactyly, syndactyly, facial capillary hemangiomas, hydrocephalus, intestinal, cardiovascular and renal anomalies, and eye, ear, and cranial nerve defects. Other malformations include facial and oculomotor paresthesias, other ocular defects, anal stenoses, vaginal and uterine defects, and heart malformations which are usually fatal. Mortality at or shortly after birth has been reported to be ~40%.<sup>3</sup>

**Contraception:**

**Women** must use **effective contraception** for at least **1 month before, during, and 1 month after** thalidomide therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or because patient has been naturally postmenopausal for at least 24 months. Two reliable forms of contraception must be used simultaneously unless continuous abstinence from reproductive heterosexual intercourse is the chosen method.<sup>43</sup>

Before starting treatment, women of childbearing potential must have a **pregnancy test** immediately (e.g., within 5 days) prior to beginning therapy and regularly (e.g., monthly) during therapy. A pregnancy test is required for all women are under the age of 50 years old and who have<sup>44</sup>:

- not undergone a hysterectomy,
- not been naturally postmenopausal for 24 consecutive months,
- experienced artificial menopause (e.g., chemotherapy or radiation induced menopause) or
- tubal ligation.

A pregnancy test should be performed if a patient misses her period or if there is any abnormality in menstrual bleeding. If pregnancy does occur during thalidomide therapy, thalidomide must be discontinued immediately.

**Men** should not have sex without an **effective birth control** method with a woman who is able to bear children because thalidomide is present in semen.<sup>41</sup> A condom must be used every time a man has sex with a female partner.

Avoid drugs that may **interact** with oral contraceptives (e.g., carbamazepine, HIV-protease inhibitors, rifabutin, rifampin) in women taking thalidomide. If these drugs must be used concurrently with thalidomide, use two other reliable methods (other than oral contraceptives).<sup>3</sup>

**Breastfeeding** is not recommended due to the potential secretion into breast milk.

**SIDE EFFECTS:**

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they

were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in <b>bold, italics</b>	
blood/bone marrow febrile neutropenia	anemia (5-12%, severe < 4%) <sup>8,45</sup>
	leukopenia (5-25%) <sup>8,45</sup>
	thrombocytopenia (severe < 4%) <sup>8</sup>
cardiovascular (arrhythmia)	sinus bradycardia (rare) <sup>46</sup>
cardiovascular (general)	edema (may be symptomatic) (4-22%) (dose-related) <sup>8,19,45</sup>
coagulation	venous thrombosis (up to 27% when used with other chemotherapy) <sup>47-50</sup> ; see paragraph following <b>Side Effects</b> table
	arterial thrombosis (rare) <sup>47</sup> ; see paragraph following <b>Side Effects</b> table
constitutional symptoms	<b>weakness or fatigue</b> (mild-moderate) (8– 48%) <sup>8,19,45</sup>
dermatology/skin	cutaneous ulcers (rare) <sup>51</sup>
	rash < 50% of body (16-26%) <sup>8,10</sup> ; > 50% of body (rare) <sup>19</sup>
	toxic epidermal necrolysis (Steven-Johnson syndrome) (rare) <sup>45,52,53</sup>
endocrine	gynecomasty (rare) <sup>54</sup>
	hypothyroidism (rare) <sup>12,55</sup>
gastrointestinal	<i>emetogenic potential: low-moderate</i>
	<b>constipation</b> (4-59%) <sup>8,10,19,45</sup>
	nausea (11-23%) <sup>8</sup>
hepatic	hepatitis (rare) <sup>56</sup>
	hyperlipidemia (5-9%) <sup>45</sup>
metabolic/laboratory	tumor lysis syndrome (rare) <sup>57</sup>
neoplasms	second primary malignancies, including acute myeloid leukemia and myelodysplastic syndrome <sup>40,42</sup> (<1%)
neurology	<b>ataxia (mild)</b> (16-22%) <sup>8</sup>
	dizziness (mild) (4-28%) <sup>8,45</sup>
	insomnia with withdrawal <sup>58</sup>
	mood alterations or depression (mild) (16-22%) <sup>8</sup>
	<b>neuropathy – sensory</b> (numbness, tingling) (8-28%) <sup>8,10,45</sup> ; see paragraph following <b>Side Effects</b> table
	<b>somnolence</b> (5-43%) <sup>8,45</sup> ; see paragraph following <b>Side Effects</b> table
	tremors (mild) (10-22%) <sup>8</sup>
pain	mild-moderate headache (10-14%) <sup>8,45</sup>
sexual/reproductive function	amenorrhea (transient) (rare) <sup>59-61</sup> ; see paragraph following <b>Side Effects</b> table
	teratogenicity (common) <sup>3,6</sup>

**Somnolence and fatigue** usually improves with continued use or dose reduction.<sup>8</sup> Thalidomide is best started at bedtime to minimize somnolence as its effects usually wear off by morning. For example, it can be started at 200mg

at bedtime and titrated up by adding equally to the bedtime and a morning dose, ie, the bedtime dose remains 200mg higher than the morning dose.<sup>62</sup>

**Peripheral neuropathy** occurs due to axonal degeneration without demyelination and affects mainly the lower limbs. It can be quite painful<sup>62</sup> and is characterized by a stocking-glove distribution and begins in the feet with paresthesias, progresses to the hands with a burning sensation and muscle cramps. Motor disability does not usually occur although may present late in the course of neuropathy and is generally reversible. The risk and severity of sensory neuropathy may depend on the cumulative dose, particularly when it exceeds 20 g.<sup>63</sup> Thalidomide should be discontinued when neuropathy is present in early stages as sensory effects may not be reversible if thalidomide is continued with ongoing symptoms. Thalidomide should be restarted only if the neuropathy returns to baseline levels.<sup>3</sup>

**Amenorrhea**, usually transient, has rarely been reported.<sup>59-61,64</sup> Average onset is about 14 months and persists for the duration of therapy. Menses resumed 2-3 months after stopping thalidomide. Serum follicle-stimulating hormone (FSH) levels were in the post-menopausal range and returned to normal when thalidomide was stopped. There was no change in serum luteinizing hormone (LH) or prolactin levels.<sup>59</sup>

Patients receiving thalidomide are at increased risk of **thromboembolic events**. Venous (e.g., DVT, PE) and arterial events (e.g., myocardial infarction, cerebrovascular accident, transient ischemic attack) have been reported and are sometimes fatal. Risk appears greatest during the first 5 months of treatment. Thrombotic risk may be increased in patients with a history of thromboembolic events or when thalidomide is used in combination with other chemotherapy and/or steroids, as well as erythropoietic agents, hormone replacement therapy, and hormonal contraceptives. Other risk factors associated with arterial thrombotic events include underlying malignancy, age over 65 years, male gender, hyperlipidemia, hypertension, diabetes, obesity, renal disease, and tobacco use. Patients and healthcare professionals should be observant for signs and symptoms of thrombotic events and seek care if patients develop symptoms. Consider thromboprophylaxis (including LMWH or warfarin), particularly in patients with additional thrombotic risk factors.<sup>40,65</sup>

#### INTERACTIONS:

No known drug interactions. See also **Contraception** under **SPECIAL PRECAUTIONS** for drugs that can affect contraception.

#### SUPPLY AND STORAGE:

**Oral:** Celgene Inc. supplies thalidomide as 50 mg, 100 mg, and 200 mg capsules. Store at room temperature.<sup>66</sup>

#### DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy.

#### Adults:

BC Cancer usual dose noted in **bold, italics**

Oral:

***starting at 200 mg PO once daily, and increasing to the maximum tolerated dose (usual dose range 50-800 mg/day);*** preferably one hour after meals

Dose may be given as once daily or divided as follows<sup>67</sup>:

Total dose (mg)	Schedule
50	50 mg once daily
100	50 mg twice daily
150	50 mg three times daily
200	50 mg four times daily
Above 200 mg dose, divide into four doses throughout the day	

BC Cancer usual dose noted in ***bold, italics***

<i>Dosage in myelosuppression:</i>	no information found
<i>Dosage in renal failure:</i>	no adjustment required
<i>Dosage in hepatic failure:</i>	no adjustment required
<i>Dosage in dialysis</i>	no information found

**Children:**

Oral: No information found. Not generally recommended for use in children.

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