DRUG NAME: Lenalidomide

SYNONYM(S):

COMMON TRADE NAME(S): REVLIMID®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Lenalidomide is an immunomodulator, a structural and functional analogue of thalidomide. While they remain to be fully characterized, multiple mechanisms of action have been identified, including increasing hemoglobin expression by erythroid cells, inhibiting proliferation of certain hematopoietic tumour cells, enhancing T cell, NK cell and NK T cell number and activity, and inhibiting angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of microvessels.[1] It inhibits production of proinflammatory cytokines e.g., TNF and TNF alpha, and increases production of IL-2 and IFN gamma.[2] One possible molecular target of lenalidomide is the Akt core signaling pathway, with which some of these effects are associated.[1] Lenalidomide is an immunosuppressive agent.[1]

PHARMACOKINETICS:

Oral Absorption	rapid; unaffected by food; time to peak: 0.6-1.5 h (myeloma patients: 0.5-4 h)[3]	
Distribution	cross blood brain barrier?	no information found
	volume of distribution	76-85 L
	plasma protein binding	23-29%
Metabolism	probably via non-enzymatic hydrolysis	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily renal[1]; AUC increased by 56% in patients with mild renal impairment[3]	
	urine	~67%; primarily as unchanged drug
	feces	yes
	terminal half life	3 h
	clearance	240-302 mL/min

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:

*Myelodysplastic syndromes

Other uses:

Multiple myeloma[2]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:

- history of hypersensitivity reaction to lenalidomide or thalidomide[1]

- women of childbearing potential or sexually mature males unless they can comply with the criteria of the RevAid® program[1]

Caution:

- do NOT ***give blood nor donate semen*** while taking lenalidomide and for 4 weeks after stopping[1]
- optimal control of ***thyroid function*** is recommended prior to treatment for patients with history of thyroid disease, as hypo- and hyperthyroidism are reported with lenalidomide[4]
- solid organ ***transplant rejection*** has been reported; onset may be acute[5-8]

Special populations: Incidence of serious side effects is significantly higher (60 vs. 35%) in patients greater than **65 years** of age. Older patients are also more likely to discontinue treatment than younger patients (30 vs. 10%).[1]

Carcinogenicity: no information found

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test.[1] Lenalidomide is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1]

Fertility: no information found

Pregnancy: FDA Pregnancy Category X.[3] Studies in animals or humans have shown fetal abnormalities, or there is evidence of fetal risk based on human experience, or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. Contraindicated in women who are or may become pregnant.

Contraception: **Females** of childbearing potential may be treated provided that adequate contraception i.e., two simultaneous effective methods of birth control, are used.[1] Contraceptive measures are indicated even in females with a history of infertility.[2] Only those who have undergone hysterectomy, bilateral oophorectomy, or who are naturally postmenopausal i.e., have had no menses for >24 consecutive months, do not need to observe contraceptive measures.[2] Avoid drugs that may interact with oral contraceptives; if these drugs must be used concurrently, use two other reliable forms of contraception (other than oral contraceptives). Contraceptive measures should be used throughout treatment and continued for 4 weeks following the last dose of lenalidomide.

Pregnancy must be excluded in females of childbearing potential i.e., negative **pregnancy test** within 10-14 days prior and again within the 24 h immediately prior to the first dose, using a reliable pregnancy test with the sensitivity to detect human chorionic gonadotropin concentrations of at least 50 mIU/mL.[1,2] Testing should be repeated during treatment as required by the RevAid® Program.

During treatment, and for 4 weeks following, **males** must use latex condoms during any sexual contact with females of childbearing potential.[1,2]

Breastfeeding is not recommended due to the potential secretion into breast milk.[1]

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.[9]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	allergic dermatitis (1-5%, severe <1%)
	hypersensitivity (1-5%, severe <1%)
	transfusion reaction (1-5%, severe <15%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
auditory/hearing	tinnitus (1-5%, severe <1%)
blood/bone marrow/ febrile neutropenia	***anemia*** (20%, severe 14%)
	febrile neutropenia (6%, severe 6%)
	granulocytopenia (1-5%, severe 1%)
	leukopenia (10%, severe 8%)
	neutropenia (64%, severe 62%); see paragraph following **Side Effects** table
	pancytopenia (1-5%, severe 3%)
	polycythemia (1-5%, severe <1%)
	thrombocytopenia (62%, severe 53%); see paragraph following **Side Effects** table
cardiovascular (arrhythmia)	atrial fibrillation (1-5%, severe 3%)
	bradycardia (1-5%, severe <1%)
	palpitations (5%, severe <1%)
	tachycardia (1-5%, severe <1%)
cardiovascular (general)	angina pectoris (1-5%, severe <1%)
	congestive heart failure (1-5%, severe 1-3%)
	hypertension (7%, severe 4%)
	hypotension (1-5%, severe <1%)
constitutional symptoms	***fatigue*** (36%, severe 6%)
	feeling cold, peripheral coldness (1-5%, severe <1%)
	fever (24%, severe 3%)
	inflammation, not otherwise specified (1-5%, severe <1%)
	insomnia, sleep disorders (1-12%, severe <1%)
	lethargy, malaise (1-5%, severe <1%)
	night sweats (10%, severe <1%)
	somnolence (1-5%, severe <1%)
	weight gain, weight loss (1-6%, severe <1%)
dermatology/skin	abrasion (1-5%, severe <1%)
	alopecia (1-5%, severe <1%)
	contusion (8%, severe <1%)
	decubitus ulcer (1-5%, severe <1%)
	discolouration (1-5%, severe <1%)
	drug reaction with eosinophilia and systemic symptoms (DRESS)[4] (<1%)
	dry skin (14%, severe <1%)
	ecchymosis (6%, severe <1%)
	erythema (6%, severe <1%)
	exanthem (1-5%, severe <1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	flushing (1-5%, severe <1%)
	impaired healing (1-5%, severe <1%)
	irritation (1-5%, severe <1%)
	laceration (1-5%, severe <1%)
	mucosal inflammation (1-5%, severe <1%)
	neutrophilic dermatosis (Sweet Syndrome)[10] (<1%)
	pruritis (44%, severe 3%)
	rash (36%, severe 6%)
	Stevens-Johnson syndrome[4] (<1%)
	sweating (9%, severe 1%)
	toxic epidermal necrolysis[4] (<1%)
	urticaria (1-5%, severe <1%)
endocrine	diabetes mellitus (1-5%, severe <1%)
	hyperthyroidism (1-10%)[4]
	hypothyroidism (9%, severe 1%)[4]
gastrointestinal	*emetogenic potential:* low[11]
	abdominal distension, tenderness (1-5%, severe <1%)
	ageusia (1-5%, severe <1%)
	anorexia (12%, severe 1%)
	colonic polyp (1-5%, severe <1%)
	constipation (25%, severe <1%)
	diarrhea (54%, severe 5%); loose stools (8%, severe <1%)
	diverticulitis, diverticulum (1-5%, severe <1%)
	dry mouth (7%, severe <1%)
	dysgeusia (6%, severe <1%)
	dyspepsia (1-5%, severe <1%)
	dysphagia (1-5%, severe 1%)
	flatulence (5%, severe <1%)
	gastritis, gastroenteritis, gastrointestinal upset (1-5%, severe <1%)
	gastroesophageal reflux disease (1-5%, severe <1%)
	hemorrhoids (1-5%, severe <1%)
	intestinal spasm (1-5%, severe <1%)
	mouth ulceration (1-5%, severe <1%)
	nausea (26%, severe 5%)
	stomatitis, aphthous stomatitis (1-5%, severe <1%)
	vomiting (11%, severe 2%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
hemorrhage	conjunctival, eye bleeding (1-5%, severe <1%)
	epistaxis (16%, severe 1%)
	gingival bleeding (1-5%, severe <1%)
	hematoma (1-5%, severe <1%)
	hemorrhoidal, rectal (1-5%, severe <1%)
	metrorrhagia, vaginal (1-5%, severe <1%)
	petechiae (1-5%, severe <1%)
hepatobiliary/pancreas	hepatotoxicity[12,13]; see paragraph following **Side Effects** table
	splenomegaly (1-5%, severe <1%)
immune system	acute graft versus host disease[5]
	solid organ transplant rejection[5-8]; onset possible within 1-3 cycles
infection	abscess, including skin, subcutaneous, tooth (1-5%, severe <1%)
	bacteremia (1-5%, severe 1%)
	cellulitis (6%, severe 1%)
	ear infection (1-5%, severe <1%)
	fungal infection, including skin, vaginosis, oral candidiasis (1-5%, severe 1%)
	influenza (7%, severe 2%)
	influenza-like illness (1-5%, severe <1%)
	pneumonia (12%, severe 10%)
	rash (1-5%, severe <1%)
	respiratory tract infection (1-5%, severe 1%)
	sepsis (1-5%, severe 4%)
	sinusitis (11%, severe 1%)
	upper respiratory tract infection (18%, severe 1%)
	urinary tract infection (13%, severe1%)
	viral infection (1-5%, severe <1%)
lymphatics	lymphadenopathy (1-5%, severe <1%)
	edema, pitting edema (1-12%, severe <1%)
	peripheral edema (24%, severe 2%)
metabolic/laboratory	alkaline phosphatase increase (1-5%, severe <1%)
	ALT increase (8%, severe 3%)
	AST increase (1-5%, severe 1%)
	blood glucose increase (1-5%, severe <1%)
	blood thyroid stimulating hormone increase (1-10%)[4]
	dehydration (1-5%, severe 1%)
	gout (1-5%, severe <1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hemochromatosis (1-5%, severe <1%)
	hypercholesterolemia (1-5%, severe <1%)
	hypo- or hyperbilirubinemia (1-5%, severe <1%)
	hypocalcemia (1-5%, severe <1%)
	hypokalemia (12%, severe 4%)
	hypomagnesemia (6%, severe <1%)
	hyponatremia (1-5%, severe 2%)
	serum creatinine increase (1-5%, severe 1%)
	uric acid increase (1-5%, severe <1%)
musculoskeletal	asthenia (15%, severe 2%)
	arthritis, aggravated arthritis, periarthritis (1-5%, severe <1%)
	limb injury (1-5%, severe <1%)
	muscle cramp (19%, severe 2%)
	muscle spasm (1-5%, severe <1%)
	osteopenia, osteoporosis (1-5%, severe <1%)
	rib fracture (1-5%, severe <1%)
	rigors (6%, severe <1%)
	spinal compression fracture (1-5%, severe <1%)
	stiffness (1-5%, severe <1%)
neurology	anxiety, agitation, mental status changes/mood alteration (1-5%, severe <1%)
	depression (6%, severe <1%)
	dizziness (22%, severe 3%)
	fall (10%, severe 1%)
	hypoasthesia (7%, severe <1%)
	neuropathy, peripheral neuropathy (1-6%, severe <1%)
	paraesthesia (5%, severe <1%)
	progressive multifocal leukoencephalopathy[14]; see paragraph following **Side Effects** table
	psychosomatic disease (1-5%, severe 1%)
	sciatica (1-5%, severe <1%)
	sensory disturbance (1-5%, severe <1%)
	syncope (1-5%, severe 1%)
	transient ischemic attack (1-5%, severe 2%)
	tremor (1-5%, severe <1%)
	vasovagal attack (1-5%, severe <1%)
	vertigo (1-5%, severe <1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
ocular/visual	blurred vision, conjunctivitis, diplopia, dry eye, eyelid edema, eye pruritis, macular degeneration, visual disturbance (1-5%, severe <1%)
pain	abdominal pain (1-14%, severe 1%)
	arthralgia (25%, severe 2%)
	back pain (24%, severe 5%)
	bone pain (1-5%, severe <1%)
	chest pain (6%, severe 2%)
	chest wall pain (1-5%, severe <1%)
	dental discomfort (1-5%, severe <1%)
	ear discomfort, ear pain (1-5%, severe <1%)
	flank pain (1-5%, severe <1%)
	foot pain (6%, severe <1%)
	headache (20%, severe 1%)
	jaw pain (1-5%, severe <1%)
	limb pain (13%, severe 1%)
	musculoskeletal pain (1-5%, severe <1%)
	myalgia (10%, severe <1%)
	neck pain (1-5%, severe <1%)
	oral pain (1-5%, severe <1%)
pulmonary	asthma (1-5%, severe <1%)
	bronchitis (12%, severe <1%)
	COPD exacerbation (1-5%, severe <1%)
	cough (1-23%, severe <1%); sometimes productive
	crackles (1-5%, severe <1%)
	dyspnea (1-22%, severe 1-2%)
	hoarseness (1-5%, severe <1%)
	hypoxia (1-5%, severe 1%)
	infiltration (1-5%, severe <1%)
	nasal, sinus congestion (1-5%, severe <1%)
	nasopharyngitis, pharyngitis (18-27%, severe 1%)
	pleural effusion (1-5%, severe 2%)
	pneumonitis (1-5%, severe 1%)
	pulmonary edema (1-5%, severe 1%)
	pulmonary hypertension (1-5%, severe 1%)
	rhinitis, rhinorrhea (1-7%, severe <1%)
renal/genitourinary	cystitis (1-5%, severe <1%)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	dysuria (7%, severe <1%)
	renal failure (1-5%, severe 2%)
secondary malignancy	acute leukemia (5%, severe 5%)
	basal cell carcinoma, squamous cell carcinoma (1-5%, severe <1%)
syndromes	hypersensitivity pneumonitis-like syndrome[1,15]
	irritable bowel syndrome (1-5%, severe <1%)
	multi-organ failure (1-5%, severe 1%)
vascular	arterial aneurysm (1-5%, severe <1%)
	deep vein thrombosis (5%, severe 5%); see paragraph following **Side Effects** table
	pulmonary embolism (severe 3%); see paragraph following **Side Effects** table
	thrombophlebitis (1-5%, severe <1%)

Adapted from standard reference[1] unless specified otherwise.

Hepatic failure, sometimes fatal, has occurred in patients receiving lenalidomide in combination with dexamethasone. Acute hepatic failure, toxic hepatitis, cytolytic hepatitis, and cholestatic hepatitis have been reported. The mechanism of this reaction is unknown; however, pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Periodic monitoring of liver enzymes is recommended. Hold lenalidomide upon elevation of liver enzymes; resumption of treatment at a lower dose may be considered after liver enzymes have returned to baseline.[13]

Neutropenia and ***thrombocytopenia*** were reversible and not cumulative.[1] In patients with myelodysplastic syndromes, monitor CBC weekly for the first 8 weeks of therapy and at least monthly thereafter[1,2]; in patients with multiple myeloma, less frequent monitoring, every 2 weeks for the first 12 weeks of therapy and at least monthly thereafter, has been recommended.[2]

Cases of ***progressive multifocal leukoencephalopathy*** (PML) have been reported with lenalidomide in combination with immunosuppressive therapy, including dexamethasone. PML is sometimes fatal. Lenalidomide should be held in patients with new or worsening neurological, cognitive, or behavioural signs/symptoms until a diagnosis of PML can be excluded. If PML is confirmed, lenalidomide should be permanently discontinued.[14]

Thromboembolic events: various risk factors have been identified including newly diagnosed disease, use in a combination regimen including doxorubicin or high dose dexamethasone, immobilization, infection, history of thromboembolism, prior thalidomide treatment, and concurrent erythropoietin use.[16] Prophylactic anticoagulation may be appropriate, and has been recommended for patients being treated with lenalidomide plus dexamethasone.[16,17]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
digoxin[1]	maximum digoxin concentration increased by 14%; AUC not significantly changed	unknown	monitor digoxin levels periodically
warfarin[1]	no effect		

In vitro, lenalidomide is not a substrate, inhibitor, or inducer of cytochrome P450 enzymes.[1]

See ***Contraception*** under **Special Precautions** for special warnings relating to drugs which may interact with drugs used for contraception.

SUPPLY AND STORAGE:

Oral: Celgene Inc. supplies 2.5 mg, 5 mg,10 mg, 15 mg, 20 mg, and 25 mg capsules. Capsules contain lactose. Store at room temperature.[5]

Additional information: Available only through a controlled distribution program called RevAid®. Only prescribers and pharmacists registered with the program are able to prescribe and dispense to patients who are registered and meet all the conditions of the RevAid® program.[1] Further information available at www.RevAid.ca or by calling 1-888-RevAid1.

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

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

Oral:

Cycle length:

4 weeks[14,18-21]: ***25 mg PO once daily for 21 consecutive days*** starting on day 1.
Administer with food or on an empty stomach.

4 weeks[14,22-24]: ***10 mg PO once daily for 21 consecutive days*** starting on day 1.
Administer with food or on an empty stomach.

n/a[2,16,25,26]: ***10 mg*** (range 5-25 mg) ***PO once daily***.
Administer with food or on an empty stomach.

Concurrent radiation: has been used[27]

Dosage in myelosuppression[1-3]*:* refer to protocol by which patient is being treated; in the absence of a protocol, the following guidelines may be used:

*Dose adjustment for **myelosuppression** developed **WITHIN 4 weeks of starting at 10 mg daily**:*

Counts at baseline (x 10^9/L)			Counts during treatment			Recommended course
platelets		ANC	platelets		ANC	
≥100	And /Or	≥1	<50	And /Or	<0.75	Interrupt treatment. Resume at 5 mg daily when platelets recover to ≥50 and/or ANC ≥1
60-99		<1	≤50% of baseline		<0.5	Interrupt treatment. Resume at 5 mg daily when platelets recover to ≥50 and/or ANC ≥1
50-59						Interrupt treatment. Resume at 5 mg daily when platelets recover to ≥30 and/or ANC ≥0.5

*Dose adjustment for **myelosuppression** developed **AFTER 4 weeks of starting at 10 mg daily:***

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

Counts during treatment (x 10^9/L)			Recommended course
platelets		ANC	
<30 or <50 with platelet transfusion	And/Or	<0.5 x 7 days or associated with fever ≥38.5°C	Interrupt treatment. Resume at 5 mg daily when platelets recover to ≥30 (without hemostatic failure) and ANC recovers to ≥0.5

*Dose adjustment for **myelosuppression** developed during treatment at **reduced dose of 5 mg daily**:*			
Counts during treatment (x 10^9/L)			Recommended course
platelets		ANC	
<30 or <50 with platelet transfusion	And/Or	<0.5 x 7 days or associated with fever ≥38.5°C	Interrupt treatment. Resume at 5 mg every other day when platelets recover to ≥30 (without hemostatic failure) and ANC recovers to ≥0.5

*Dose adjustment for **thrombocytopenia** developed **after starting at 25 mg daily**:*	
Counts during treatment (x 10^9/L)	Recommended course
if count falls <30	Interrupt treatment; check CBC weekly
if count returns to ≥30 following an interruption	Resume at 15 mg daily
for each subsequent fall <30	Interrupt treatment
if count returns to ≥30 following interruption for subsequent falls <30	Resume at a dose 5 mg less than previous dose (minimum dose 5 mg daily)

*Dose adjustment for **neutropenia** developed **after starting at 25 mg daily**:*	
Counts during treatment (x 10^9/L)	Recommended course
if count falls <1	Interrupt treatment, add filgrastim, check CBC weekly
if count returns to ≥1 following an interruption and no other toxicity is present	Resume at 25 mg daily
if count returns to ≥1 following an interruption and if other toxicity is present	Resume at 15 mg daily
for each subsequent fall to <1	Interrupt treatment
if count returns to ≥1 following interruption in treatment for subsequent falls to <1	Resume at a dose 5 mg less than the previous dose (minimum dose 5 mg daily)

Dosage in renal failure:

Patients with **myelodysplastic syndrome**[1-3,28]:	
Creatinine clearance (mL/min)	**Dose**
≥60	10 mg daily
30-59	5 mg daily
<30, not requiring dialysis	5 mg every other day
<30, requiring dialysis	5 mg three times a week following each dialysis

Patients with **multiple myeloma**[2,3,28]:	
Creatinine clearance (mL/min)	**Dose**
≥60	25 mg daily
30-59	10 mg daily*
<30, not requiring dialysis	15 mg every other day
<30, requiring dialysis	5 mg daily; take following dialysis on dialysis days
*dose may be increased to 15 mg daily after 2 cycles in patients who have not responded to treatment.	

Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{}$

Serum Creatinine in µmol/L

* For males N=1.23; for females N=1.04

Dosage in hepatic failure: no information found for starting dose adjustment
Dosage in dialysis: starting dose adjustment as per renal dosing[14]

Children:

Oral: safety and effectiveness in patients <18 years old have not been established[1]

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