DRUG NAME: Pomalidomide

SYNONYM(S):

COMMON TRADE NAME(S): POMALYST®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Pomalidomide is an analogue of thalidomide and has multiple modes of action.[1] Pomalidomide enhances T-cell- and natural killer (NK) cell-mediated immunity. It inhibits angiogenesis and the production of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). *In vitro,* pomalidomide inhibits proliferation and induces apoptosis of tumour cells. Pomalidomide can also inhibit the proliferation of lenalidomide-resistant multiple myeloma cells and is synergistic with dexamethasone to induce apoptosis in both lenalidomide-sensitive and lenalidomide-resistant cells.[1,2]

PHARMACOKINETICS:

Oral Absorption	73%; rapid[2]; time to peak: 2-3 h	
Distribution	distributed in semen: 67% of plasma level	
	cross blood brain barrier?	no information found
	volume of distribution	62-138 L
	plasma protein binding	12-44%
Metabolism	substrate of P-glycoprotein; metabolism mainly by CYP 1A2 and CYP 3A4, and non-CYP dependent hydrolysis; 3 predominant metabolites (unnamed) in urine	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	extensive hepatic metabolism prior to excretion	
	urine[1,2]	73%; 2% as unchanged drug
	feces[1,2]	15%; 8% as unchanged drug
	terminal half life	7.5 h
	clearance	7-10 L/h

Adapted from standard reference[1] unless specified otherwise.

USES:

Primary uses:
*Multiple myeloma

Other uses:

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to thalidomide or lenalidomide[1]
- pregnant or breastfeeding women[1]
- women of childbearing potential or sexually mature males[3] unless they can comply with the criteria of the controlled distribution program, RevAid®[1]

Caution:
- patients should ***not give blood*** or ***donate sperm*** during treatment and for at least 4 weeks after discontinuation of therapy[1]
- risk of ***thromboembolic events*** may be increased with concurrent use with erythropoietic agents, hormone replacement therapy, or hormonal contraceptives; prophylactic antithrombotic therapy may be recommended[1]
- ***starting dose adjustments*** are recommended in patients with ***hepatic impairment or severe renal impairment requiring dialysis***[4]

Special populations:
Females of childbearing potential (FCBP) may be treated provided that they comply with the conditions of the RevAid® program. These conditions include using adequate contraception i.e., abstinence or two simultaneous and effective methods of birth control. Contraceptive measures are indicated even in females with a history of infertility and those who have amenorrhea and must be used for at least 4 weeks before starting treatment, during dose interruptions, continually during treatment, and for at least 4 weeks after discontinuation of therapy. Hormonal contraceptives are not recommended as they are associated with an increase risk of thromboembolic events.[1] ***Male*** patients must comply with the conditions of the RevAid® program, and use a condom during any sexual contact with FCBP even if they have undergone a vasectomy. Condoms must be used during treatment, dose interruptions, and for at least 4 weeks after discontinuation of therapy.[1]

Carcinogenicity: Second primary malignancies, including acute myeloid leukemia (AML), have been reported in patients receiving pomalidomide.[1,3]

Mutagenicity: Not mutagenic in Ames test or clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[1]

Fertility: A decrease in number of viable embryos and an increase in post-implantation loss have been reported in animal studies.[1]

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.
A reduced number of viable embryos and an increase in post-implantation loss were observed in developmental studies in animals. Pomalidomide was teratogenic when given during the period of major organogenesis, including such developmental malformations as absent urinary bladder and thyroid gland, fusion and misalignment of vertebral elements, and increased cardiac and limb anomalies. Pomalidomide is an analogue of thalidomide, a known human teratogen that causes severe and life-threatening birth defects. Because the malformations seen in animals treated with pomalimide are similar to those observed in humans following exposure to thalidomide during pregnancy, the teratogenic effect of pomalidomide in humans cannot be ruled out.[1] Pregnancy must be excluded in FCBP, i.e., two negative pregnancy tests prior to starting treatment, as well as subsequent tests throughout treatment as required by the RevAid® program.[1]

Breastfeeding is not recommended due to the potential secretion into breast milk. Pomalidomide has been detected in the milk of lactating rats.[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.[5] **Incidence data in the Side Effects table is based on combination therapy with dexamethasone.**

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic	***anemia*** (38-52%, severe 2-31%)[1,2,6,7]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
system/ febrile neutropenia	leucopenia (11-13%, severe 2-9%)[1,2,6,7]
	lymphopenia (4%, severe 2-4%)[1,2,7]
	neutropenia (45-52%, severe 22-48%)[1,2,6,7]
	thrombocytopenia (25-30%, severe 9-22%)[1,2,6,7]
	febrile neutropenia (3-10%, severe 2-8%)[1,2,6]
cardiac	atrial fibrillation (2-3%, severe 1%)[1,2]
ear and labyrinth	vertigo (3%, severe 1%)
gastrointestinal	*emetogenic potential: low*[8]
	constipation (19-36%, severe 2%)[1,2,6]
	diarrhea (18-34%, severe 1%)[1,2,6]
	nausea (12-36%, severe 1%)[1,2,6]
	vomiting (8-14%, severe 1%)[1,2]
general disorders and administration site conditions	asthenia (3-16%, severe 1-6%)[1,2,6,7]
	chills (1-9%)[1,2]
	fatigue (28-55%, severe 5-11%)[1,2,6,7]
	general physical health deterioration (9%, severe 5%)
	pain (2%, severe 1%)
	peripheral edema (13-23%, severe 1%)[1,2,6]
	pyrexia (19-27%, severe 1-3%)[1,2,6]
hepatobiliary	hepatotoxicity (<1%)[4]; including acute liver injury, hepatic failure, and cytolytic hepatitis
infections and infestations	bronchitis (8-10%, severe 1%)[1,6]
	cellulitis (1%, severe 1%)
	infection (3-68%, severe 1-24%)[1,6]
	nasopharyngitis (6%)
	pneumonia (3-23%, severe 2-15%)[1,2,6,7]
	respiratory tract infection (3-32%, severe 1-2%)[1,2,6]
	sepsis (2-6%, severe 2-6%)[1,2,7]
	urinary tract infection (5-8%, severe 1-2%)[1,2,7]
investigations	creatinine increased (1-15%, severe 6%)[1,2,7]
	hyperbilirubinemia (<1%)[4]
	weight loss (1-14%)[1,2]
	weight increase (1-5%)[1,2]
metabolism and nutrition	appetite decrease (10-22%, severe 1%)[1,2,6]
	dehydration (4%, severe 1-5%)[1,2,7]
	hypercalcemia (6-21%, severe 2-10%)[1,2,6,7]
	hyperglycemia (5-12%, severe 3%)[1,2]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hyperkalemia (3%, severe 2%)
	hyperuricemia (3%, severe 1%)
	hypocalcemia (1-6%)[1,2]
	hypokalemia (7-10%, severe 3%)[1,2]
	hyponatremia (2-10%, severe 2%)[1,2]
musculoskeletal and connective tissue	arthralgia (5-16%, severe <1%)[1,2]
	back pain (15-32%, severe 1-14%)[1,2,6,7]
	bone pain (12-17%, severe 1-7%)[1,2,6]
	limb pain (4%, severe 1%)
	muscle spasms (10-19%, severe <1%)[1,2]
	musculoskeletal pain/chest pain (1-22%, severe 1%)[1,2]
neoplasms	***second primary malignancies***; see paragraph following **Side Effects** table
nervous system	depressed level of consciousness (1%, severe 1%)
	dizziness (9-20%, severe 1%)[1,2,6]
	headache (5-13%)[1,2]
	peripheral neuropathy (10-18%, severe 1%)[1,2]
	syncope (2%, severe 1%)
	tremor (5-9%, severe 1%)[1,2]
psychiatric	anxiety(1-11%)[1,2]
	confusion (4-12%, severe 2-7%)[1,2,7]
	insomnia (7-10%, severe 1%)[1,2,6]
renal and urinary	hematuria (1-5%)[4]
	incontinence (1-5%)[4]
	pollakiuria (1-5%)[4]
	renal failure (4-15%, severe 3-8%)[1,2,7]
	urinary retention (1-5%)[1,2]
reproductive system and breast disorders	pelvic pain (2%, severe 1%)
respiratory, thoracic and mediastinal	cough (14-20%, severe <1%)[1,2,6]
	dyspnea (17-34%, severe 1-8%)[1,2,6,7]
	epistaxis (9-15%, severe <1%)[1,2,6]
skin and subcutaneous tissue	dry skin (1-9%)[1,2]
	hyperhidrosis (1-6%)[1,2]
	night sweats (1-5%)[1,2]
	pruritus (7-15%)[1,2]
	rash (7-22%, severe 1%)[1,2]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
vascular	***deep vein thrombosis*** (1-5%)[1,2]
	pulmonary embolism (1-3%, severe 1%)[1,2]

Adapted from standard reference[1] unless specified otherwise.

Side Effects occur more frequently in the first two cycles of treatment. Hold pomalidomide for non-hematologic grade 3 or 4 adverse reactions. Treatment may resume once adverse reactions have improved to grade 2 or better; restart pomalidomide at 1 mg less than the previous dose. If grade 3 or 4 adverse reactions occur after dose reduction to 1 mg PO once daily, stop treatment.[1]

Second primary malignancies have been associated with pomalidomide. Acute myeloid leukemia has been reported in patients receiving pomalidomide as investigational therapy for uses other than multiple myeloma.[3] Invasive solid cancers and non-invasive (basal cell) skin cancers were reported in clinical trials.[6]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
fluvoxamine ***AND*** ketoconazole[1]	increase plasma level of pomalidomide by 105%	pomalidomide undergoes CYP 1A2 and CYP 3A4 metabolism; fluvoxamine inhibits the CYP 1A2 pathway, AND ketoconazole inhibits the CYP 3A4/5 pathway.	avoid concurrent use with strong CYP 1A2 inhibitors AND strong CYP3A4 inhibitors ***together***.
ketoconazole[1]	no clinical effect on pomalidomide plasma level		
carbamazepine[1]	no clinical effect on pomalidomide plasma level		

Strong CYP 1A2 inhibitors may increase pomalidomide plasma levels; monitor patient for adverse effects.[1]

Cigarette smoking may reduce pomalidomide plasma levels due to CYP 1A2 induction and lead to reduced efficacy of pomalidomide.[1]

P-glycoprotein inhibitors and strong CYP 3A4/5 inhibitors or inducers do not affect pomalidomide plasma levels; therefore, clinically significant interactions are not expected.[1] However, concurrent use of strong CYP 1A2 inhibitors AND strong CYP 3A4 inhibitors together in combination with pomalidomide have demonstrated a significant increase in pomalidomide plasma level; therefore, these combinations should be avoided with pomalidomide.[1]

SUPPLY AND STORAGE:

Oral: Celgene Inc. supplies pomalidomide as 1 mg, 2 mg, 3 mg, and 4 mg capsules. Store at room temperature.[1]

Additional information[1]: Pomalidomide is 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. Further information is 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*:**

BCCA usual dose noted in ***bold, italics***

Oral[1,9]:

Cycle Length: 4 weeks

4 mg (range 1-4 mg) PO once daily for 21 consecutive days, starting on day 1.

Administer with food or on an empty stomach.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, the following adjustments have been recommended[1]:

Toxicity	Dose Modification
neutropenia • each occurrence of ANC < 0.5 x 10^9/L, or • febrile neutropenia (fever ≥ 38.5ºC and ANC < 1 x 10^9/L)	• hold treatment until ANC ≥1 x 10^9/L, then resume treatment at 1 mg less than the previous dose. • consider G-CSF (Granulocyte-Colony Stimulating Factor) if clinically indicated.
thrombocytopenia • each occurrence of platelets < 25 x 10^9/L	• hold treatment until platelets ≥ 50 x 10^9/L, then resume treatment at 1 mg less than the previous dose.

Dosage in renal failure: starting dose adjustment is recommended in patients with severe renal impairment (CrCl <30 mL/min) requiring dialysis[4]; modify according to protocol by which patient is being treated

if no guideline is available, the following adjustment is suggested[4]:

Creatinine clearance (mL/min)	Dose
<30, requiring dialysis	75%

calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

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

Dosage in hepatic failure: starting dose adjustment is recommended in patients with mild, moderate, or severe hepatic impairment[4]; modify according to protocol by which patient is being treated

if no guideline is available, the following adjustment is suggested[4]:

Degree of impairment	Dose
mild to moderate (Child-Pugh A or B)	75%
severe (Child-Pugh C)	50%

BCCA usual dose noted in ***bold, italics***

Dosage in dialysis:

Cycle Length:

starting dose adjustment is recommended in patients with severe renal impairment (CrCl <30 mL/min) requiring dialysis[4]; modify according to protocol by which patient is being treated

if no guideline is available, the following adjustment is suggested[4]:

Creatinine clearance (mL/min)	Dose
<30, requiring dialysis	75%

calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times \text{weight in kg}}{\text{serum creatinine in micromol/L}}$

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

hemodialysis: on dialysis days, take pomalidomide following dialysis[4]

Children: no information found

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