

Drug Monograph

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A - Drug Name

pomalidomide

COMMON TRADE NAME(S): Pomalyst®

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B - Mechanism of Action and Pharmacokinetics

Pomalidomide is a derivative of thalidomide, an immunomodulatory and antineoplastic agent. It enhances T-cell and NK cell-mediated immunity and inhibits production of pro-inflammatory cytokines by monocytes. It has also demonstrated apoptotic and anti-angiogenic effects *in vitro*.

Absorption	Exposure increases in an approximately dose-proportional manner. Accumulation is minimal following multiple doses. High fat and high-calorie meal slows the rate of absorption but has minimal effect on extent of absorption.	
	Bioavailability	At least 73% after a single dose
	Peak plasma levels	2-3 hours after the dose
Distribution	PPB	12-44%
Metabolism	By multiple pathways including CYP-mediated metabolism and non-CYP dependent hydrolysis	
Elimination	Mainly excreted by the kidneys	
	Half-life	7.5h (multiple myeloma patients)

Urine	73% (2% unchanged)
Feces	15% (8% unchanged)

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C - Indications and Status

Health Canada Approvals:

- Multiple myeloma

Refer to the product monograph for a full list and details of approved indications.

Notes:

Pomalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Adverse effects presented in the table were based on an open-label phase 3 study in patients with relapsed and refractory multiple myeloma receiving pomalidomide plus low-dose dexamethasone. Severe adverse events from other studies or post-marketing may also be included.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Atrial fibrillation (3%)	E
	Cardiotoxicity (<5%)	E D
	Hypertension (<5%) (or hypotension)	E
	Venous thromboembolism (<5%)	E
Dermatological	Alopecia (<5%)	E D

	Rash (7%) (may be severe)	E
	Stevens-Johnson syndrome (rare)	E
	Toxic epidermal necrolysis (rare)	E
Gastrointestinal	Anorexia (10%)	E
	Constipation (19%)	E
	Diarrhea (18%)	E
	Mucositis (<5%)	E
	Nausea, vomiting (12%)	I
General	Edema (13%)	E
	Fatigue (28%)	E
Hematological	Myelosuppression ± infection, bleeding (46%) (42% severe)	E
Hepatobiliary	↑ LFTs (<5%) (may be severe)	E
Hypersensitivity	DRESS syndrome (rare)	E
	Hypersensitivity (<5%) (may be severe)	I
Infection	Infection (11%) (including atypical, viral reactivation)	E
Metabolic / Endocrine	Abnormal electrolyte(s) (7%) (↓ PO ₄ , ↑/↓ K, ↑/↓ Ca, ↓ Na, ↓ Mg)	E
	Hypothyroidism (rare)	E D
	Tumor lysis syndrome (rare)	E
Musculoskeletal	Musculoskeletal pain (15%)	E
Neoplastic	Secondary malignancy (<5%) (including non-melanoma skin cancers)	L
Nervous System	Confusion (4%)	E
	Dizziness (9%)	E
	Headache (5%)	E
	Insomnia (8%)	E
	Leukoencephalopathy (PML) (rare)	E
	Peripheral neuropathy (11%)	E
	Vertigo (3%)	E
Ophthalmic	Cataract (<5%) (or blurred vision)	E D
	Conjunctivitis (<5%)	E
Renal	Renal failure (4%)	E D
Respiratory	Cough, dyspnea (17%)	E
	Pneumonitis (<1%)	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 reports are **myelosuppression, infection, edema and fatigue**, and occur most commonly in the first two cycles.

In clinical trials, fatal **infections** were reported in 11 (4%) of patients on pomalidomide, dexamethasone and bortezomib, compared to 3 (1.1%) of patients on bortezomib and dexamethasone. Atypical infections have also been reported, including viral reactivation such as **hepatitis B reactivation**, some with progression to acute hepatic failure and may be fatal.

Cases of **progressive multifocal leukoencephalopathy** (PML) has been reported and may be fatal. Consider PML in the differential diagnosis of new or worsening neurological, cognitive or behavioural signs or symptoms.

Pomalidomide is associated with an increased risk of **thromboembolism** especially in patients taking hormones (HRT, contraceptives), erythropoietin, or in patients with an increased risk or past history of thromboembolism.

Tumour lysis syndrome has been reported and may be fatal. Patients at risk (e.g. high tumour burden) should have appropriate prophylaxis and be monitored closely.

Severe hypersensitivity reactions and rashes have been reported, including Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), angioedema and anaphylaxis. **DRESS** (Drug Rash with Eosinophilia and Systemic Symptoms) syndrome has also been reported, with rash, eosinophilia, and systemic involvement (e.g. fever, lymphadenopathy, elevated transaminases, renal insufficiency, pneumonitis, myocarditis and/or pericarditis).

Markedly elevated liver enzymes and **hepatic failure**, including fatal cases, have been observed in clinical trials.

Cases of **pneumonitis / interstitial lung disease** (ILD) have been observed in clinical trials.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the [hepatitis B virus screening and management](#) guideline.

Pomalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

Women of child bearing potential must have two negative pregnancy tests before initiating treatment.

Prophylactic antithrombotics, such as low dose aspirin, low molecular weight heparins or warfarin, are recommended.

Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

Start treatment only if ANC $\geq 1 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$.

Adults:

In combination with dexamethasone and bortezomib*:

Q21 days: Pomalidomide 4 mg PO daily on Days 1-14

*refer to the regimen monograph for dexamethasone and bortezomib dosing

In combination with dexamethasone*:

Q28 days: Pomalidomide 4 mg PO daily on Days 1-21

*refer to the regimen monograph for dexamethasone dosing

Dosage with Toxicity:

Dose Level	Pomalidomide Dose (mg/day)
0	4
-1	3
-2	2
-3	1
-4	Discontinue

Toxicity			Dose of Pomalidomide*
ANC ($10^9/L$) < 0.5 or Febrile neutropenia (fever $\geq 38.5^{\circ}C$ and ANC < 1)	or	Platelets ($10^9/L$) < 25	Hold, monitor CBC weekly, consider G-CSF. Restart* after recovery with 1 dose level ↓.
Grade 2 or 3 skin rash			Hold or discontinue. Resume if benefit outweighs potential risk.
Grade 4 rash or rash with exfoliation, bullae or purpura, angioedema, anaphylaxis, or suspected SJS/TEN/DRESS			Discontinue.
Grade 3 or 4 non-hematologic/organ toxicities			Hold until recovery* then ↓ 1 dose level. Consider discontinuing if grade 4.
Acute onset or worsening of pulmonary symptoms			Hold and investigate for pneumonitis. Resume only after an evaluation of the benefits and risks.
PML			Hold and investigate. Discontinue if confirmed.

*Do not re-start until ANC returns to $\geq 1 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$, and non-hematological toxicities resolve to \leq grade 2.

Dosage with Hepatic Impairment:

Pomalidomide is primarily metabolized in the liver. Hepatic impairment results in a 51-72% increase in drug exposure.

The starting dose should be adjusted as follows:

Hepatic Impairment*	Pomalidomide Starting Dose (mg/day)
Child-Pugh class A or B	3
Child-Pugh class C	2

*Product monograph states that use should be avoided in patients with serum bilirubin > 1.5 x ULN and AST/ALT > 3 x ULN.

Dosage with Renal Impairment:

Pomalidomide and its metabolites are renally excreted. Pomalidomide is dialysable.

The starting dose should be adjusted for severe impairment requiring dialysis, as follows:

Creatinine Clearance (mL/min)	Pomalidomide Starting Dose (mg/day)
< 30 requiring dialysis	3 (taken after dialysis)

Dosage in the elderly:

No dose adjustment for pomalidomide is required based on age. No overall differences in effectiveness were observed.

Patients > 65 years were observed to have higher incidences of infection and pneumonia than younger patients; dexamethasone holds or reductions may be required. Dose of dexamethasone should be reduced by 50% in patients > 75 years.

There is limited information in patients over 75 years old.

Children:

Safety and efficacy have not been established in patients less than 18 years old.

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F - Administration Guidelines

Pomalidomide may only be prescribed and dispensed by physicians and pharmacists registered with a controlled distribution program. Patients must also be registered and meet all conditions of the program.

- Capsule should be swallowed whole with a glass of water. Do not crush or open the capsule.
- Doses may be administered with or without food.
- Missed dose: If less than 12 hours has passed since the missed dose, the dose may be taken. If more than 12 hours has passed since the missed dose, skip this dose and take the next one at its usual time the next day. Do not give a double dose to make up for a missed one.
- On dialysis days, administer pomalidomide after the completion of hemodialysis due to possible significant decrease in drug exposure.
- Females who could become pregnant or who plan to become pregnant can handle pomalidomide capsules if they are using latex gloves.
- Store at room temperature (15-30°C) in original package in order to protect from light.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug, any of its components, or to thalidomide or lenalidomide
- Patients who are pregnant, at risk of becoming pregnant, or are breastfeeding (Refer to Pregnancy and Lactation section)
- Male patients unable to comply with required contraceptive measures

Other Warnings/Precautions:

- Avoid use in patients with active / history of hepatitis A, B, or C.
- Avoid use in patients taking other immunosuppressive treatments, to reduce the risk of developing serious infections.
- Patients should not donate blood or semen while taking pomalidomide, during treatment interruptions, and for 4 weeks after treatment cessation.

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- Use with caution and consider prophylaxis when used in combination with corticosteroids or thrombogenic agents, such as hormones and erythropoietin or in patients with risk factors for arterial or venous thromboembolism (e.g. hypertension, hyperlipidemia, previous history of thromboembolism, or taking other agents that increase thromboembolic risk).
 - Use with caution in patients with pre-existing \geq grade 2 neuropathy.
 - Use with caution when operating machinery, or when driving, as confusion, fatigue, depressed level of consciousness and dizziness may occur with treatment.
 - Use with caution in patients with significant cardiac dysfunction (i.e. CHF NYHA Class III or IV, MI within 12 months, unstable or poorly controlled angina) as pomalidomide use has not been studied in these patients. Atrial fibrillation has occurred, especially in patients with pre-existing cardiac disease or cardiac risk factors.
 - In clinical trials, increased mortality was observed when pembrolizumab was added to dexamethasone and a thalidomide analogue.

Other Drug Properties:

- Carcinogenicity: Yes
- Immunosuppressive: Yes

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes

Pomalidomide is **contraindicated in pregnancy and in males and females of childbearing potential who do not comply with the contraception conditions of the controlled distribution program.**

Females of childbearing potential (including those who normally do not use contraception due to a history of infertility, and those who have amenorrhea) must be capable of understanding and complying with the patient registration, education, and safety requirements of the program, regular pregnancy testing and the use of two simultaneous contraception methods. Contraception must be started at least **4 weeks** prior to starting treatment, continued during dose interruptions, during treatment and for at least **4 weeks** following the cessation of pomalidomide.

Hormonal contraceptives are not recommended due to the increased risk of thromboembolism. If pregnancy occurs during treatment, pomalidomide must be discontinued and patient referred to a gynecologist/obstetrician for evaluation and counseling.

Male patients must be capable of understanding and complying with the patient registration, education, and safety requirements of the controlled distribution program, including mandatory contraceptive measures for men (condoms should be used even with vasectomized males) as pomalidomide is present in semen and exposure would harm a developing fetus.

Refer to the controlled distribution program for full details.

- Breastfeeding: Contraindicated
- Fertility effects: Probable

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H - Interactions

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A4, with minor contributions from CYP2C19 and CYP2D6. It is a substrate of P-glycoprotein.

Cigarette smoking may reduce the efficacy of pomalidomide.

Co-administration of multiple doses of pomalidomide (up to 4 mg) with dexamethasone 20-40 mg had no effects on the pharmacokinetics of pomalidomide.

Co-administration of pomalidomide with a strong CYP3A4/P-gp inhibitor (e.g. ketoconazole) or strong CYP3A4 inducer (e.g. carbamazepine), had no clinically relevant effect on pomalidomide exposure.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP1A2 inhibitors (e.g. ciprofloxacin, fluvoxamine)	↑ pomalidomide exposure	↓ metabolism of pomalidomide	Avoid strong inhibitors if possible. If not possible to avoid, reduce pomalidomide dose by 50%.
CYP1A2 inducers (e.g. montelukast), cigarette smoking	↓ pomalidomide concentration and/or efficacy	↑ metabolism of pomalidomide	Avoid if possible; monitor for reduced effects of pomalidomide.
Agents that increase thromboembolic risk (e.g. erythropoietic agents, hormone replacement therapy, oral contraceptives)	↑ risk of thromboembolism	Additive	Avoid.

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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.

Refer to the [hepatitis B virus screening and management](#) guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline, weekly for the first 8 weeks then monthly thereafter
Liver function tests	Baseline and at each visit
Renal function tests	Baseline and at each visit
Controlled distribution program requirements regarding pregnancy tests for women of child-bearing potential	Before starting, during treatment and for at least 4 weeks after discontinuation
Clinical toxicity assessment for infection, bleeding, hypersensitivity, thromboembolism, secondary malignancies, pneumonitis, hepatitis, TLS, neurological and skin effects	At each visit

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

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J - Supplementary Public Funding

Exceptional Access Program ([EAP Website](#))

- pomalidomide - For patients with relapsed and/or refractory multiple myeloma, according to specific criteria
- pomalidomide - In combination with isatuximab and dexamethasone for relapsed or refractory multiple myeloma, according to specific criteria

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K - References

Lacy MQ, McCurdy AR. Pomalidomide. Blood 2013;122(14):2305-9.

Lacy MQ, Allred JB, Gertz MA, Hayman SR, Short KD, Buadi F, et al. Pomalidomide plus low dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of 2 dosing strategies in dual-refractory disease. Blood 2011;118(11):2970-2975.

Product Monograph: Pomalyst (pomalidomide). Celgene Inc. (Canada), February 2, 2021.

San Miguel J et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM- 003): a randomized, open-label, phase 3 trial. Lancet Oncol 2013;14:1055-66.

July 2023 Updated EAP funding info

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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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