

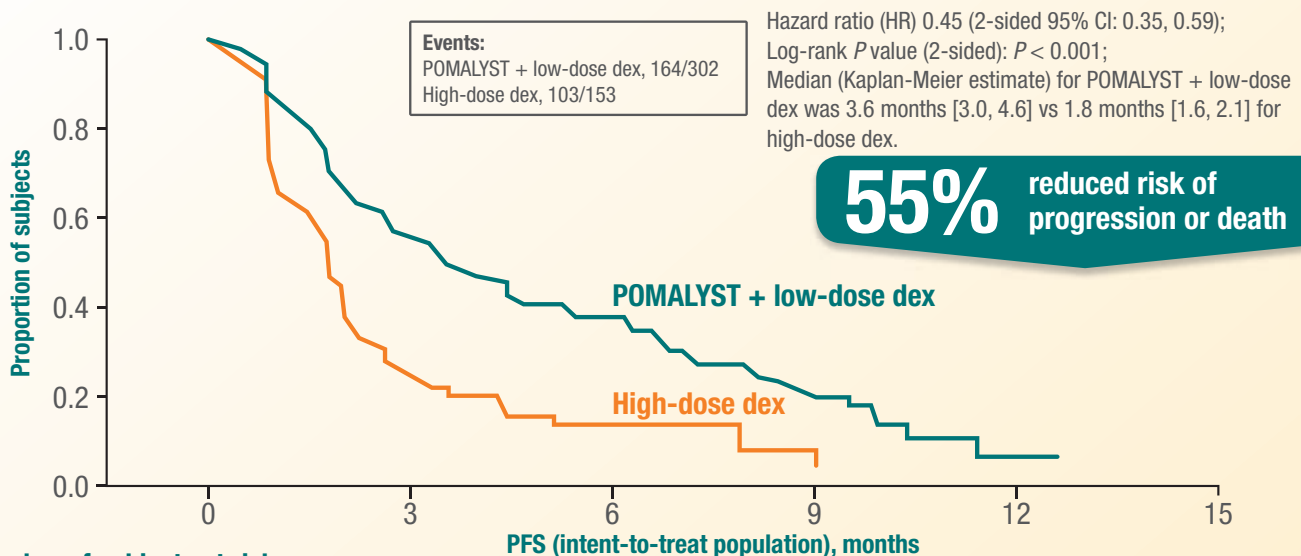
June 2015 — Celgene Corporation is pleased to announce that POMALYST® (pomalidomide) + low-dose dexamethasone (dex) delivered significantly longer progression-free survival (PFS) vs high-dose dex in a phase 3 clinical trial.¹

POMALYST is a thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Trial Highlights^{1,2}

The MM-003 trial was a phase 3, multicenter, randomized, open-label study comparing POMALYST + low-dose dex to high-dose dex in adult patients with relapsed and refractory multiple myeloma (MM). All subjects had received at least 2 prior treatment regimens, including lenalidomide and bortezomib, and demonstrated disease progression on or within 60 days of the last therapy. Patients with creatinine clearance ≥ 45 mL/min qualified for the trial. The POMALYST + low-dose dex group received 4 mg POMALYST orally on days 1 to 21 of each 28-day cycle, while dex 40 mg was administered once per day on days 1, 8, 15, and 22 of a 28-day cycle. The high-dose dex arm received dex 40 mg once per day on days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. Patients >75 years started treatment with dex 20 mg using the same schedule. Treatment was continued until disease progression. The primary end point was PFS based on International Myeloma Working Group (IMWG) criteria. The key secondary end point was overall survival (OS).

POMALYST + low-dose dex delivered significantly longer PFS vs high-dose dex (intent-to-treat population)¹



Number of subjects at risk

	0	3	6	9	12	15
POMALYST + low-dose dex	302	107	43	15	1	0
High-dose dex	153	21	6	2	0	—

PFS was based on the assessment by the Independent Review Adjudication Committee (IRAC) review at the final PFS analysis. Data cutoff: September 7, 2012.

IMPORTANT SAFETY INFORMATION

WARNING: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

- POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.

POMALYST is only available through a restricted distribution program called POMALYST REMS®.

Please see Important Safety Information throughout and full Prescribing Information, including Boxed WARNINGS.

IMPORTANT SAFETY INFORMATION (cont'd)

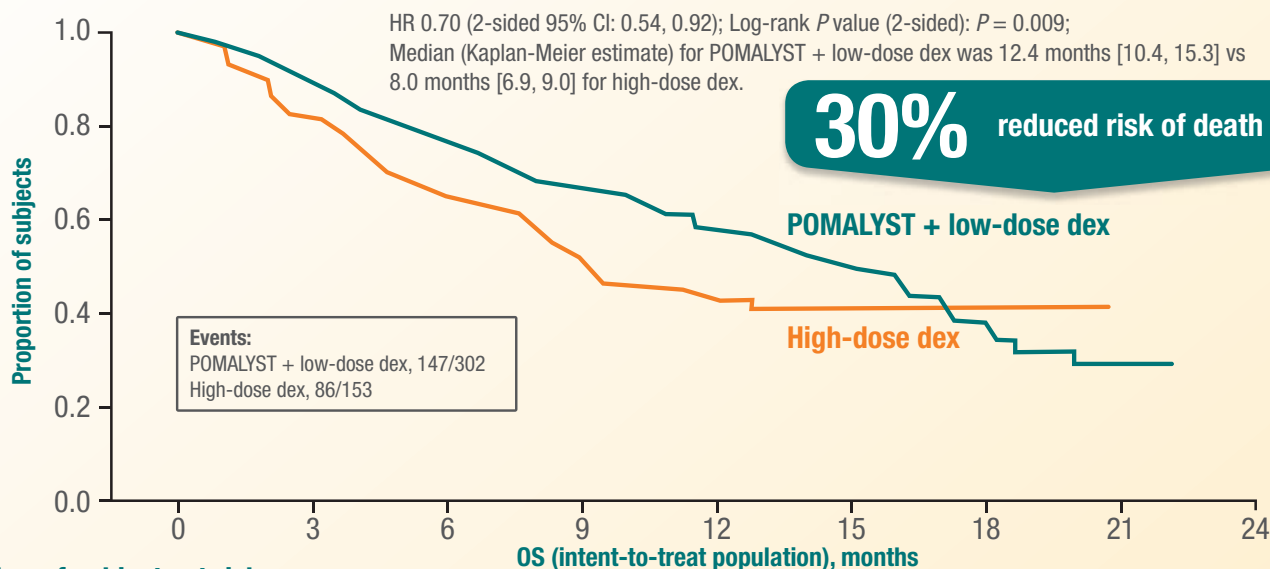
- Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment.

POMALYST is only available through a restricted distribution program called POMALYST REMS®.

Venous and Arterial Thromboembolism

- Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Prophylactic antithrombotic measures were employed in clinical trials. Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors.

POMALYST + low-dose dex delivered significantly longer OS vs high-dose dex (intent-to-treat population)¹



Number of subjects at risk

POMALYST + low-dose dex	302	248	199	126	71	32	12	1	0
High-dose dex	153	112	84	44	24	11	3	0	—

OS was based on the assessment by the Independent Review Adjudication Committee (IRAC) review at the final OS analysis. Data cutoff: March 1, 2013.

- The difference in OS was statistically significant¹
- 53% of patients in the high-dose dex arm subsequently received POMALYST¹

Adverse Reactions

The most common Grade 3/4 hematologic adverse reactions in the POMALYST + low-dose dex and high-dose dex groups were neutropenia (48% vs 16%, respectively), anemia (33% vs 37%, respectively), and thrombocytopenia (22% vs 26%, respectively). Grade 3/4 non-hematologic adverse events in the POMALYST + low-dose dex and high-dose dex groups included pneumonia (13% vs 8%, respectively), bone pain (7% vs 5%, respectively), and fatigue (5% vs 6%, respectively). Incidence of pneumonia (any grade) was similar in the 2 arms (15% vs 11%, respectively). The development of neutropenia did not appear to affect the incidence of infections, and Grade 3/4 infections occurred in 30% of patients in the POMALYST + low-dose dex group vs 24% in the high-dose dex group.^{1,2}

In the POMALYST + low-dose dex arm, 67% of patients had a dose interruption of POMALYST, and the median time to the first dose interruption of POMALYST was 4.1 weeks. Dose reduction of POMALYST occurred in 27% of patients, with a median time to the first dose reduction of 4.5 weeks. Eight percent of patients discontinued POMALYST due to adverse reactions.¹

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 **Pomalyst**
(pomalidomide) capsules
1 · 2 · 3 · 4 mg

Dose Modifications for Hematologic Toxicities¹

Neutropenia	
When absolute neutrophil counts (ANC):	Recommended course
Fall to <500/mcL or febrile neutropenia (fever $\geq 38.5^{\circ}\text{C}$ and ANC <1000 per mcL) Return to ≥ 500 per mcL	Interrupt POMALYST treatment, follow CBC weekly Resume POMALYST at 3 mg daily
For each subsequent drop <500 per mcL Return to ≥ 500 per mcL	Interrupt POMALYST treatment Resume POMALYST at 1 mg less than the previous dose. If toxicities occur after dose reductions to 1 mg, then discontinue POMALYST.

Thrombocytopenia	
When platelet counts:	Recommended course
<25,000 per mcL Return to >50,000 per mcL	Interrupt POMALYST treatment, follow CBC weekly Resume POMALYST at 3 mg daily
For each subsequent drop <25,000 per mcL Return to $\geq 50,000$ per mcL	Interrupt POMALYST treatment Resume POMALYST at 1 mg less than the previous dose. If toxicities occur after dose reductions to 1 mg, then discontinue POMALYST.

- To begin a new cycle of POMALYST, the patient's neutrophil count must be at least 500 per mcL and the platelet count must be at least 50,000 per mcL
- If toxicities occur after dose reductions to 1 mg, then discontinue POMALYST
- Neutropenia was the most frequently reported Grade 3/4 adverse reaction, followed by anemia and thrombocytopenia
- Neutropenia of any grade was reported in 51% of patients in both trials
 - Rate of Grade 3/4 neutropenia was 46%
 - Rate of febrile neutropenia was 8%
- Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter

Other Toxicities in MM

Permanently discontinue POMALYST for angioedema, skin exfoliation, bullae, or any other severe dermatologic reaction.

For other Grade 3/4 toxicities, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion.

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Dosage Forms and Strengths¹

POMALYST is available in 1-, 2-, 3-, and 4-mg capsules.

NDC and Pricing

NDC	Dosage Strength	Package Size	Wholesale Acquisition Cost ^{3,a}
59572-504-21	4 mg	21 capsules	\$11,756.39
59572-504-00	4 mg	100 capsules	\$55,982.82
59572-503-21	3 mg	21 capsules	\$11,756.39
59572-503-00	3 mg	100 capsules	\$55,982.82
59572-502-21	2 mg	21 capsules	\$11,756.39
59572-502-00	2 mg	100 capsules	\$55,982.82
59572-501-21	1 mg	21 capsules	\$11,756.39
59572-501-00	1 mg	100 capsules	\$55,982.82

^aWholesale acquisition cost (WAC) as of June 25, 2015. WAC does not include any discounts, including prompt pay discounts, or any other price concession that may be provided to a buyer.

ICD-9 Diagnostic Code

The ICD-9 diagnostic code for multiple myeloma is 203.0.⁴

Storage

POMALYST should be stored at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F).

Important Information About POMALYST REMS[®] Program

Because of the embryo-fetal risk, POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called “**POMALYST REMS[®]**.”

Required components of the **POMALYST REMS[®]** program include the following:

- Prescribers must be certified with the **POMALYST REMS[®]** program by enrolling and complying with the REMS requirements
- Patients must sign a Patient-Physician Agreement Form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements
- Pharmacies must be certified with the **POMALYST REMS[®]** program, must only dispense to patients who are authorized to receive POMALYST, and comply with REMS requirements

Further information about the **POMALYST REMS[®]** program is available at www.CelgeneRiskManagement.com or by telephone at **1-888-423-5436**.

POMALYST is only available through a restricted distribution program called POMALYST REMS[®].

Please see Important Safety Information throughout and full Prescribing Information, including Boxed WARNINGS.



Pomalyst[®]
(pomalidomide) capsules
1 · 2 · 3 · 4 mg

Dosage and Administration for POMALYST¹

Females of reproductive potential must have negative pregnancy testing and use contraception methods before initiating POMALYST.

- The recommended starting dose of POMALYST is 4 mg once daily orally on days 1 through 21 of repeated 28-day cycles until disease progression
- POMALYST should be given in combination with dexamethasone
 - In the MM-003 trial, the POMALYST + low-dose dex group received dex 40 mg once per day on days 1, 8, 15, and 22 of a 28-day cycle. Patients >75 years started treatment with dex 20 mg using the same schedule
 - Patients in the high-dose dex arm received dex 40 mg once per day on days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. Patients >75 years started treatment with dex 20 mg, using the same schedule
- POMALYST may be taken with water. Patients should not break, chew, or open the capsules
- POMALYST should be taken without food (at least 2 hours before or 2 hours after a meal)
- Monitor CBCs every week for the first 8 weeks and monthly thereafter
- Patients may require dose interruptions and/or modifications
- Monitor liver function tests monthly. Stop POMALYST upon elevation of liver enzymes and evaluate. After return to baseline values, treatment at a lower dose may be considered

For a list of pharmacies certified in the **POMALYST REMS[®]** program, visit www.Celgene.com/PharmacyNetwork. For more information, or if you have any questions about obtaining POMALYST, visit www.CelgeneRiskManagement.com or contact your local Celgene representative.

Financial Assistance

- Celgene Patient Support[®] is a free service that can help you and your patients access Celgene medications. Co-pays for POMALYST are reduced to \$25 for your eligible patients with commercial insurance. We can also connect your Medicare and Medicaid patients to third-party organizations that have funding to help with deductibles, co-pays/coinsurance, or insurance premiums. In addition, uninsured patients may qualify for free medication
- Your Celgene Patient Support[®] Specialist can also provide you and your patients with assistance obtaining insurance approval for POMALYST by conducting a benefits investigation, guiding the prior authorization/precertification process, and providing appeals support
- Call your specialist at **1-800-931-8691** for more detailed information on our support services

Visit www.pomalyst.com to download the full Prescribing Information.

Visit CelgenePatientSupport.com to learn about the services that are available to help your patients access POMALYST.

IMPORTANT SAFETY INFORMATION (cont'd)

CONTRAINDICATIONS: Pregnancy

POMALYST can cause fetal harm and is contraindicated in females who are pregnant. If POMALYST is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity

- **Females of Reproductive Potential:** Must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy
- **Males:** Pomalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Males must not donate sperm
- **Blood Donation:** Patients must not donate blood during treatment with POMALYST and for 1 month following discontinuation of POMALYST therapy because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST

POMALYST REMS® Program

Because of the embryo-fetal risk, POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called “**POMALYST REMS®**.” Prescribers and pharmacies must be certified with the program; patients must sign an agreement form and comply with the requirements. Further information about the **POMALYST REMS®** program is available at www.CelgeneRiskManagement.com or by telephone at 1-888-423-5436.

Venous and Arterial Thromboembolism: Venous thromboembolic events (DVT and PE) and arterial thromboembolic events (ATE) (myocardial infarction and stroke) have been observed in patients treated with POMALYST. In Trial 2, where anticoagulant therapies were mandated, thromboembolic events occurred in 8.0% of patients treated with POMALYST and low-dose dexamethasone (Low-dose Dex) vs 3.3% treated with high-dose dexamethasone. Venous thromboembolic events (VTE) occurred in 4.7% of patients treated with POMALYST and Low-dose Dex vs 1.3% treated with high-dose dexamethasone. Arterial thromboembolic events include terms for arterial thromboembolic events, ischemic cerebrovascular conditions, and ischemic heart disease. Arterial thromboembolic events occurred in 3.0% of patients treated with POMALYST and Low-dose Dex vs 1.3% treated with high-dose dexamethasone. Patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking).

Hematologic Toxicity: In Trials 1 and 2 in patients who received POMALYST + Low-dose Dex, neutropenia (46%) was the most frequently reported Grade 3/4 adverse reaction, followed by anemia and thrombocytopenia. Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification.

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with POMALYST. Elevated levels of alanine aminotransferase and bilirubin have also been observed in patients treated with POMALYST. Monitor liver function tests monthly. Stop POMALYST upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Hypersensitivity Reactions: Angioedema and severe dermatologic reactions have been reported. Discontinue POMALYST for angioedema, skin exfoliation, bullae, or any other severe dermatologic reactions, and do not resume therapy.

Dizziness and Confusional State: In Trials 1 and 2 in patients who received POMALYST + Low-dose Dex, 14% experienced dizziness and 7% a confusional state; 1% of patients experienced Grade 3 or 4 dizziness and 3% experienced a Grade 3 or 4 confusional state. Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.

Neuropathy: In Trials 1 and 2, patients who received POMALYST + Low-dose Dex experienced neuropathy (18%) and peripheral neuropathy (~12%). In Trial 2, 2% of patients experienced Grade 3 neuropathy.

Risk of Second Primary Malignancies: Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

Tumor Lysis Syndrome: Tumor lysis syndrome (TLS) may occur in patients treated with POMALYST. Patients at risk are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

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IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

Nearly all patients treated with POMALYST + Low-dose Dex experienced at least one adverse reaction (99%). In Trial 2, the most common adverse reactions included neutropenia (51.3%), fatigue and asthenia (46.7%), upper respiratory tract infection (31%), thrombocytopenia (29.7%), pyrexia (26.7%), dyspnea (25.3%), diarrhea (22%), constipation (21.7%), back pain (19.7%), cough (20%), pneumonia (19.3%), edema peripheral (17.3%), peripheral neuropathy (17.3%), bone pain (18%), nausea (15%), and muscle spasms (15.3%). Grade 3 or 4 adverse reactions included neutropenia (48.3%), thrombocytopenia (22%), and pneumonia (15.7%).

DRUG INTERACTIONS

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp). Avoid the use of strong CYP1A2 inhibitors. If medically necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, reduce POMALYST dose by 50%. Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Nursing Mothers: It is not known if pomalidomide is excreted in human milk. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from POMALYST, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of POMALYST in patients under the age of 18 have not been established.

Geriatric Use: No dosage adjustment is required for POMALYST based on age. Patients >65 years of age were more likely than patients ≤65 years of age to experience pneumonia.

Renal and Hepatic Impairment: Pomalidomide is metabolized in the liver. Pomalidomide and its metabolites are primarily excreted by the kidneys. The influence of renal and hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Avoid POMALYST in patients with a serum creatinine >3.0 mg/dL. Avoid POMALYST in patients with serum bilirubin >2.0 mg/dL and AST/ALT >3.0 x ULN.

Please see full [Prescribing Information](#), including **Boxed WARNINGS.**

Report any SUSPECTED ADVERSE REACTIONS or suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 or www.fda.gov/medwatch and also to Celgene Corporation at 1-888-423-5436.

References

1. POMALYST [prescribing information]. Summit, NJ: Celgene Corporation; 2015.
2. San Miguel J, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(11):1055-1066.
3. Data on file, Celgene Corporation.
4. Centers for Medicare & Medicaid Services. ICD-9 Code Lookup. <http://www.cms.gov/medicare-coverage-database/staticpages/icd-9-code-lookup.aspx>. Accessed May 7, 2015.

POMALYST is only available through a restricted distribution program called POMALYST REMS®.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use POMALYST safely and effectively. See full prescribing information for POMALYST.

POMALYST® (pomalidomide) capsules, for oral use
Initial U.S. Approval: 2013

WARNING: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM

See full prescribing information for complete boxed warning

EMBRYO-FETAL TOXICITY

- POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe life-threatening birth defects (4, 5.1, 8.1).
- For females of reproductive potential: Exclude pregnancy before start of treatment. Prevent pregnancy during treatment by the use of 2 reliable methods of contraception (5.1, 8.6).

POMALYST is available only through a restricted program called POMALYST REMS® (5.2).

VENOUS AND ARTERIAL THROMBOEMBOLISM

- Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Antithrombotic prophylaxis is recommended (5.3).

RECENT MAJOR CHANGES

Boxed Warning	04/15
Indications and Usage (1.1)	04/15
Dosage and Administration (2.1, 2.2)	04/15
Warnings and Precautions (5.3, 5.4, 5.5, 5.6, 5.7, 5.8)	04/15
Warnings and Precautions (5.10)	05/14

INDICATIONS AND USAGE

POMALYST is a thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy (1.1).

DOSAGE AND ADMINISTRATION

4 mg per day taken orally on Days 1-21 of repeated 28-day cycles until disease progression (2.1). Refer to section 14.1 for dexamethasone dosing (14.1).

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM

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Capsules: 1 mg, 2 mg, 3 mg, and 4 mg (3)

CONTRAINDICATIONS

- Pregnancy (4)

WARNINGS AND PRECAUTIONS

- Hematologic Toxicity: Neutropenia was the most frequently reported Grade 3/4 adverse event. Monitor patients for hematologic toxicities, especially neutropenia (5.4).
- Hepatotoxicity: Hepatic failure including fatalities; monitor liver function tests monthly (5.5).
- Hypersensitivity Reactions: Angioedema and severe dermatologic reactions have been reported. Discontinue POMALYST for angioedema and severe dermatologic reactions (5.6).
- Tumor Lysis Syndrome (TLS): Monitor patients at risk of TLS (i.e., those with high tumor burden) and take appropriate precautions (5.10).

ADVERSE REACTIONS

Most common adverse reactions (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper-respiratory tract infections, back pain, and pyrexia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Celgene Corporation at 1-888-423-5436 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP1A2 Inhibitors: Avoid the use of strong CYP1A2 inhibitors unless medically necessary (2.3, 7.1, 12.3).

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing taking into consideration importance of drug to mother (8.3).
- Avoid POMALYST in patients with serum creatinine >3.0 mg/dL (8.7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2015

7.1 Drugs That May Increase Pomalidomide Plasma Concentrations
7.2 Drugs That May Decrease Pomalidomide Plasma Concentrations

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FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY and VENOUS AND ARTERIAL THROMBOEMBOLISM

Embryo-Fetal Toxicity

- **POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.**
- **Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment [see *Contraindications (4)*, *Warnings and Precautions (5.1)*, and *Use in Specific Populations (8.1, 8.6)*].**

POMALYST is only available through a restricted distribution program called POMALYST REMS [see *Warnings and Precautions (5.2)*].

Venous and Arterial Thromboembolism

- **Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with POMALYST. Prophylactic antithrombotic measures were employed in clinical trials. Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors [see *Warnings and Precautions (5.3)*].**

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

POMALYST, in combination with dexamethasone, is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Multiple Myeloma

Females of reproductive potential must have negative pregnancy testing and use contraception methods before initiating POMALYST [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*].

The recommended starting dose of POMALYST is 4 mg once daily orally on Days 1-21 of repeated 28-day cycles until disease progression. POMALYST should be given in combination with dexamethasone [see *Clinical Studies (14.1)*].

POMALYST may be taken with water. Inform patients not to break, chew, or open the capsules. POMALYST should be taken without food (at least 2 hours before or 2 hours after a meal).

2.2 Dose Adjustments for Toxicities

Table 1: Dose Modification Instructions for POMALYST for Hematologic Toxicities

Toxicity	Dose Modification
<p>Neutropenia</p> <ul style="list-style-type: none"> ANC <500 per mcL or febrile neutropenia (fever more than or equal to 38.5°C and ANC <1,000 per mcL) ANC return to more than or equal to 500 per mcL 	<ul style="list-style-type: none"> Interrupt POMALYST treatment, follow CBC weekly Resume POMALYST treatment at 3 mg daily
<ul style="list-style-type: none"> For each subsequent drop <500 per mcL Return to more than or equal to 500 per mcL 	<ul style="list-style-type: none"> Interrupt POMALYST treatment Resume POMALYST treatment at 1 mg less than the previous dose
<p>Thrombocytopenia</p> <ul style="list-style-type: none"> Platelets <25,000 per mcL Platelets return to >50,000 per mcL 	<ul style="list-style-type: none"> Interrupt POMALYST treatment, follow CBC weekly Resume POMALYST treatment at 3 mg daily
<ul style="list-style-type: none"> For each subsequent drop <25,000 per mcL Return to more than or equal to 50,000 per mcL 	<ul style="list-style-type: none"> Interrupt POMALYST treatment Resume POMALYST treatment at 1 mg less than previous dose

ANC, absolute neutrophil count

To initiate a new cycle of POMALYST, the neutrophil count must be at least 500 per mcL and the platelet count must be at least 50,000 per mcL. If toxicities occur after dose reductions to 1 mg, then discontinue POMALYST.

Permanently discontinue POMALYST for angioedema, skin exfoliation, bullae, or any other severe dermatologic reaction [see *Warnings and Precautions (5.6)*].

For other Grade 3 or 4 toxicities, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion.

2.3 Dose Adjustment for Strong CYP1A2 Inhibitors in the Presence of Strong CYP3A4 and P-gp Inhibitors

Avoid co-administration of strong inhibitors of CYP1A2. If necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, reduce POMALYST dose by 50%. No clinical efficacy or safety data exist [see *Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

POMALYST is available in the following capsule strengths:

1 mg: Dark blue opaque cap and yellow opaque body, imprinted "POML" on the cap in white ink and "1 mg" on the body in black ink

2 mg: Dark blue opaque cap and orange opaque body, imprinted "POML" on the cap and "2 mg" on the body in white ink

3 mg: Dark blue opaque cap and green opaque body, imprinted "POML" on the cap and "3 mg" on the body in white ink

4 mg: Dark blue opaque cap and blue opaque body, imprinted "POML" on the cap and "4 mg" on the body in white ink

4 CONTRAINDICATIONS

Pregnancy

POMALYST can cause fetal harm when administered to a pregnant female [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*]. POMALYST is contraindicated in females who are pregnant. Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

POMALYST is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death [see *Use in Specific Populations (8.1)*]. POMALYST is only available through the POMALYST REMS program [see *Warnings and Precautions (5.2)*].

Females of Reproductive Potential

Females of reproductive potential must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing POMALYST therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles, or every 2 weeks in women with irregular menstrual cycles [see *Use in Specific Populations (8.6)*].

Males

Pomalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm [see *Use in Specific Populations (8.6)*].

Blood Donation

Patients must not donate blood during treatment with POMALYST and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to POMALYST.

5.2 POMALYST REMS Program

Because of the embryo-fetal risk [see *Warnings and Precautions (5.1)*], POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called “**POMALYST REMS.**”

Required components of the **POMALYST REMS** program include the following:

- Prescribers must be certified with the **POMALYST REMS** program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Physician Agreement Form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [see *Use in Specific Populations (8.6)*] and males must comply with contraception requirements [see *Use in Specific Populations (8.6)*].
- Pharmacies must be certified with the **POMALYST REMS** program, must only dispense to patients who are authorized to receive POMALYST, and comply with REMS requirements.

Further information about the **POMALYST REMS** program is available at www.CelgeneRiskManagement.com or by telephone at 1-888-423-5436.

5.3 Venous and Arterial Thromboembolism

Venous thromboembolic events (deep venous thrombosis and pulmonary embolism) and arterial thromboembolic events (myocardial infarction and stroke) have been observed in patients treated with POMALYST. In Trial 2, where anticoagulant therapies were mandated, thromboembolic events occurred in 8.0% of patients treated with POMALYST and low dose-dexamethasone (Low-dose Dex), and 3.3% of patients treated with high-dose dexamethasone. Venous thromboembolic events (VTE) occurred in 4.7% of patients treated with POMALYST and Low-dose Dex, and 1.3% of patients treated with high-dose dexamethasone. Arterial thromboembolic events include terms for arterial thromboembolic events, ischemic cerebrovascular conditions, and ischemic heart disease. Arterial thromboembolic events occurred in 3.0% of patients treated with POMALYST and Low-dose Dex, and 1.3% of patients treated with high-dose dexamethasone.

Patients with known risk factors, including prior thrombosis, may be at greater risk, and actions should be taken to try to minimize all modifiable factors (e.g., hyperlipidemia, hypertension, smoking). Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors.

5.4 Hematologic Toxicity

In trials 1 and 2 in patients who received POMALYST + Low-dose Dex, neutropenia was the most frequently reported Grade 3/4 adverse reaction, followed by anemia and thrombocytopenia. Neutropenia of any grade was reported in 51% of patients in both trials. The rate of Grade 3/4 neutropenia was 46%. The rate of febrile neutropenia was 8%.

Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification [see *Dosage and Administration (2.2)*].

5.5 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with POMALYST. Elevated levels of alanine aminotransferase and bilirubin have also been observed in patients treated with POMALYST. Monitor liver function tests monthly. Stop POMALYST upon elevation of liver enzymes and evaluate. After return to baseline values, treatment at a lower dose may be considered.

5.6 Hypersensitivity Reactions

Angioedema and severe dermatologic reactions have been reported. Discontinue POMALYST for angioedema, skin exfoliation, bullae, or any other severe dermatologic reactions, and do not resume therapy [see *Dosage and Administration* (2.2)].

5.7 Dizziness and Confusional State

In trials 1 and 2 in patients who received POMALYST + Low-dose Dex, 14% of patients experienced dizziness and 7% of patients experienced a confusional state; 1% of patients experienced Grade 3 or 4 dizziness, and 3% of patients experienced Grade 3 or 4 confusional state. Instruct patients to avoid situations where dizziness or confusional state may be a problem and not to take other medications that may cause dizziness or confusional state without adequate medical advice.

5.8 Neuropathy

In trials 1 and 2 in patients who received POMALYST + Low-dose Dex, 18% of patients experienced neuropathy, with approximately 12% of the patients experiencing peripheral neuropathy. Two percent of patients experienced Grade 3 neuropathy in trial 2. There were no cases of Grade 4 neuropathy adverse reactions reported in either trial.

5.9 Risk of Second Primary Malignancies

Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

5.10 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) may occur in patients treated with pomalidomide. Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other labeling sections:

- Fetal Risk [see *Boxed Warnings, Warnings and Precautions* (5.1, 5.2)]
- Venous and Arterial Thromboembolism [see *Boxed Warnings, Warnings and Precautions* (5.3)]
- Hematologic Toxicity [see *Warnings and Precautions* (5.4)]
- Hepatotoxicity [see *Warnings and Precautions* (5.5)]
- Hypersensitivity Reactions [see *Warnings and Precautions* (5.6)]
- Dizziness and Confusional State [see *Warnings and Precautions* (5.7)]
- Neuropathy [see *Warnings and Precautions* (5.8)]
- Risk of Second Primary Malignancies [see *Warnings and Precautions* (5.9)]
- Tumor Lysis Syndrome [see *Warnings and Precautions* (5.10)]

6.1 Clinical Trials Experience

Multiple Myeloma

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In Trial 1, data were evaluated from 219 patients (safety population) who received treatment with POMALYST + Low-dose Dex (112 patients) or POMALYST alone (107 patients). Median number of treatment cycles was 5. Sixty-seven percent of patients in the study had a dose interruption of either drug due to adverse reactions. Forty-two percent of patients in the study had a dose reduction of either drug due to adverse reactions. The discontinuation rate due to adverse reactions was 11%.

In Trial 2, data were evaluated from 450 patients (safety population) who received treatment with POMALYST + Low-dose Dex (300 patients) or High-dose Dexamethasone (High-dose Dex) (150 patients). The median number of treatment cycles for the POMALYST + Low-dose Dex arm was 5. In the POMALYST + Low-dose Dex arm, 67% of patients had a dose interruption of POMALYST, the median time to the first dose interruption of POMALYST was 4.1 weeks. Twenty-seven percent of patients had a dose reduction of POMALYST, the median time to the first dose reduction of POMALYST was 4.5 weeks. Eight percent of patients discontinued POMALYST due to adverse reactions.

Tables 2 and 3 summarize the adverse reactions reported in Trials 1 and 2, respectively.

Table 2: Adverse Reactions in Any POMALYST Treatment Arm in Trial 1*

System Organ Class/Preferred Term	All Adverse Reactions $\geq 10\%$ in Either Arm		Grade 3 or 4 $\geq 5\%$ in Either Arm	
	POMALYST ^a (N=107)	POMALYST + Low-dose Dex (N=112)	POMALYST (N=107)	POMALYST + Low-dose Dex (N=112)
Number (%) of patients with at least one adverse reaction	107 (100)	112 (100)	98 (91.6)	102 (91.1)
Blood and lymphatic system disorders				
Neutropenia ^b	57 (53.3)	55 (49.1)	51 (47.7)	46 (41.1)
Anemia ^b	41 (38.3)	47 (42.0)	25 (23.4)	24 (21.4)
Thrombocytopenia ^b	28 (26.2)	26 (23.2)	24 (22.4)	21 (18.8)
Leukopenia	14 (13.1)	22 (19.6)	7 (6.5)	11 (9.8)
Febrile neutropenia ^b	<10%	<10%	6 (5.6)	3 (2.7)
Lymphopenia	4 (3.7)	17 (15.2)	2 (1.9)	8 (7.1)
General disorders and administration site conditions				
Fatigue and asthenia ^b	62 (57.9)	70 (62.5)	13 (12.1)	19 (17.0)
Edema peripheral	27 (25.2)	19 (17.0)	0 (0.0)	0 (0.0)
Pyrexia ^b	25 (23.4)	36 (32.1)	<5%	<5%
Chills	11 (10.3)	14 (12.5)	0 (0.0)	0 (0.0)
Gastrointestinal disorders				
Nausea ^b	39 (36.4)	27 (24.1)	<5%	<5%

System Organ Class/Preferred Term	All Adverse Reactions $\geq 10\%$ in Either Arm		Grade 3 or 4 $\geq 5\%$ in Either Arm	
	POMALYST ^a (N=107)	POMALYST + Low-dose Dex (N=112)	POMALYST (N=107)	POMALYST + Low-dose Dex (N=112)
Constipation ^b	38 (35.5)	41 (36.6)	<5%	<5%
Diarrhea	37 (34.6)	40 (35.7)	<5%	<5%
Vomiting ^b	15 (14.0)	16 (14.3)	<5%	0 (0.0)
Musculoskeletal and connective tissue disorders				
Back pain ^b	37 (34.6)	36 (32.1)	15 (14.0)	11 (9.8)
Musculoskeletal chest pain	25 (23.4)	22 (19.6)	<5%	0 (0.0)
Muscle spasms	23 (21.5)	22 (19.6)	<5%	<5%
Arthralgia	18 (16.8)	17 (15.2)	<5%	<5%
Muscular weakness	15 (14.0)	15 (13.4)	6 (5.6)	4 (3.6)
Bone pain	13 (12.1)	8 (7.1)	<5%	<5%
Musculoskeletal pain	13 (12.1)	19 (17.0)	<5%	<5%
Pain in extremity	8 (7.5)	16 (14.3)	0 (0.0)	<5%
Infections and infestations				
Upper respiratory tract infection	40 (37.4)	32 (28.6)	<5%	<5%
Pneumonia ^b	30 (28.0)	38 (33.9)	21 (19.6)	32 (28.6)
Urinary tract infection ^b	11 (10.3)	19 (17.0)	2 (1.9)	10 (8.9)
Sepsis ^b	<10%	<10%	6 (5.6)	5 (4.5)
Metabolism and nutrition disorders				
Decreased appetite	25 (23.4)	21 (18.8)	<5%	0 (0.0)
Hypercalcemia ^b	23 (21.5)	13 (11.6)	11 (10.3)	1 (0.9)
Hypokalemia	13 (12.1)	13 (11.6)	<5%	<5%
Hyperglycemia	12 (11.2)	17 (15.2)	<5%	<5%
Hyponatremia	12 (11.2)	14 (12.5)	<5%	<5%
Dehydration ^b	<10%	<10%	5 (4.7)	6 (5.4)
Hypocalcemia	6 (5.6)	13 (11.6)	0 (0.0)	<5%
Respiratory, thoracic and mediastinal disorders				
Dyspnea ^b	38 (35.5)	50 (44.6)	8 (7.5)	14 (12.5)

System Organ Class/Preferred Term	All Adverse Reactions $\geq 10\%$ in Either Arm		Grade 3 or 4 $\geq 5\%$ in Either Arm	
	POMALYST ^a (N=107)	POMALYST + Low-dose Dex (N=112)	POMALYST (N=107)	POMALYST + Low-dose Dex (N=112)
Cough	18 (16.8)	25 (22.3)	0 (0.0)	0 (0.0)
Epistaxis	18 (16.8)	12 (10.7)	<5%	0 (0.0)
Productive cough	10 (9.3)	14 (12.5)	0 (0.0)	0 (0.0)
Oropharyngeal pain	6 (5.6)	12 (10.7)	0 (0.0)	0 (0.0)
Nervous system disorders				
Dizziness	24 (22.4)	20 (17.9)	<5%	<5%
Peripheral neuropathy	23 (21.5)	20 (17.9)	0 (0.0)	0 (0.0)
Headache	16 (15.0)	15 (13.4)	0 (0.0)	<5%
Tremor	11 (10.3)	15 (13.4)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders				
Rash	22 (20.6)	18 (16.1)	0 (0.0)	<5%
Pruritus	16 (15.0)	10 (8.9)	0 (0.0)	0 (0.0)
Dry skin	10 (9.3)	12 (10.7)	0 (0.0)	0 (0.0)
Hyperhidrosis	8 (7.5)	18 (16.1)	0 (0.0)	0 (0.0)
Night sweats	5 (4.7)	14 (12.5)	0 (0.0)	0 (0.0)
Investigations				
Blood creatinine increased ^b	20 (18.7)	11 (9.8)	6 (5.6)	3 (2.7)
Weight decreased	16 (15.0)	10 (8.9)	0 (0.0)	0 (0.0)
Weight increased	1 (0.9)	12 (10.7)	0 (0.0)	0 (0.0)
Psychiatric disorders				
Anxiety	14 (13.1)	8 (7.1)	0 (0.0)	0 (0.0)
Confusional state ^b	13 (12.1)	15 (13.4)	6 (5.6)	3 (2.7)
Insomnia	7 (6.5)	18 (16.1)	0 (0.0)	0 (0.0)
Renal and urinary disorders				
Renal failure ^b	16 (15.0)	11 (9.8)	9 (8.4)	8 (7.1)

* Regardless of attribution of relatedness to POMALYST.

^a POMALYST alone arm includes all patients randomized to the POMALYST alone arm who took study drug; 61 of the 107 patients had dexamethasone added during the treatment period.

^b Serious adverse reactions were reported in at least 2 patients in any POMALYST treatment arm.

Data cutoff: 01 March 2013

Table 3: Adverse Reactions in Trial 2

System Organ Class/Preferred Term	All Adverse Reactions (≥5% in POMALYST + Low-dose Dex arm, and at least 2% point higher than the High-dose-Dex arm)		Grade 3 or 4 (≥1% in POMALYST + Low-dose Dex arm, and at least 1% point higher than the High-dose-Dex arm)	
	POMALYST + Low-dose Dex (N=300)	High-dose Dex (N=150)	POMALYST + Low-dose Dex (N=300)	High-dose Dex (N=150)
Number (%) of patients with at least one adverse reaction	297 (99.0)	149 (99.3)	259 (86.3)	127 (84.7)
Blood and lymphatic system disorders				
Neutropenia ^b	154 (51.3)	31 (20.7)	145 (48.3)	24 (16.0)
Thrombocytopenia	89 (29.7) ^a	44 (29.3) ^a	66 (22.0) ^a	39 (26.0) ^a
Leukopenia	38 (12.7)	8 (5.3)	27 (9.0)	5 (3.3)
Febrile neutropenia ^b	28 (9.3)	0 (0.0)	28 (9.3)	0 (0.0)
General disorders and administration site conditions				
Fatigue and asthenia	140 (46.7)	64 (42.7)	26 (8.7) ^a	18 (12.0) ^a
Pyrexia ^b	80 (26.7)	35 (23.3)	9 (3.0) ^a	7 (4.7) ^a
Edema peripheral	52 (17.3)	17 (11.3)	4 (1.3) ^a	3 (2.0) ^a
Pain	11 (3.7) ^a	3 (2.0) ^a	5 (1.7)	1 (0.7)
Infections and infestations				
Upper respiratory tract infection ^b	93 (31.0)	19 (12.7)	9 (3.0)	1 (0.7)
Pneumonia ^b	58 (19.3)	20 (13.3)	47 (15.7)	15 (10.0)
Neutropenic sepsis ^b	3 (1.0) ^a	0 (0.0) ^a	3 (1.0)	0 (0.0)
Gastrointestinal disorders				
Diarrhea	66 (22.0)	28 (18.7)	3 (1.0) ^a	2 (1.3) ^a
Constipation	65 (21.7)	22 (14.7)	7 (2.3)	0 (0.0)
Nausea	45 (15.0)	17 (11.3)	3 (1.0) ^a	2 (1.3) ^a
Vomiting	23 (7.7)	6 (4.0)	3 (1.0)	0 (0.0)
Musculoskeletal and connective tissue disorders				
Back pain ^b	59 (19.7)	24 (16.0)	15 (5.0)	6 (4.0)
Bone pain ^b	54 (18.0)	21 (14.0)	22 (7.3)	7 (4.7)
Muscle spasms	46 (15.3)	11 (7.3)	1 (0.3) ^a	1 (0.7) ^a
Arthralgia	26 (8.7)	7 (4.7)	2 (0.7) ^a	1 (0.7) ^a

System Organ Class/Preferred Term	All Adverse Reactions (≥5% in POMALYST + Low-dose Dex arm, and at least 2% point higher than the High-dose-Dex arm)		Grade 3 or 4 (≥1% in POMALYST + Low-dose Dex arm, and at least 1% point higher than the High-dose-Dex arm)	
	POMALYST + Low-dose Dex (N=300)	High-dose Dex (N=150)	POMALYST + Low-dose Dex (N=300)	High-dose Dex (N=150)
Pain in extremity	20 (6.7) ^a	9 (6.0) ^a	6 (2.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea ^b	76 (25.3)	25 (16.7)	17 (5.7)	7 (4.7)
Cough	60 (20.0)	15 (10.0)	2 (0.7) ^a	1 (0.7) ^a
Chronic obstructive pulmonary disease ^b	5 (1.7) ^a	0 (0.0) ^a	4 (1.3)	0 (0.0)
Nervous system disorders				
Peripheral neuropathy	52 (17.3)	18 (12.0)	5 (1.7) ^a	2 (1.3) ^a
Dizziness	37 (12.3)	14 (9.3)	4 (1.3) ^a	2 (1.3) ^a
Headache	23 (7.7)	8 (5.3)	1 (0.3) ^a	0 (0.0) ^a
Tremor	17 (5.7)	2 (1.3)	2 (0.7) ^a	0 (0.0) ^a
Depressed level of consciousness	5 (1.7) ^a	0 (0.0) ^a	3 (1.0)	0 (0.0)
Metabolism and nutrition disorders				
Decreased appetite	38 (12.7)	12 (8.0)	3 (1.0) ^a	2 (1.3) ^a
Hypokalemia	28 (9.3) ^a	12 (8.0) ^a	12 (4.0)	4 (2.7)
Hypocalcemia	12 (4.0) ^a	9 (6.0) ^a	5 (1.7)	1 (0.7)
Skin and subcutaneous tissue disorders				
Rash	23 (7.7)	2 (1.3)	3 (1.0)	0 (0.0)
Pruritus	22 (7.3)	5 (3.3)	0 (0.0) ^a	0 (0.0) ^a
Hyperhidrosis	15 (5.0)	1 (0.7)	0 (0.0) ^a	0 (0.0) ^a
Investigations				
Neutrophil count decreased	15 (5.0)	1 (0.7)	14 (4.7)	1 (0.7)
Platelet count decreased	10 (3.3) ^a	3 (2.0) ^a	8 (2.7)	2 (1.3)
White blood cell count decreased	8 (2.7) ^a	1 (0.7) ^a	8 (2.7)	0 (0.0)
Alanine aminotransferase increased	7 (2.3) ^a	2 (1.3) ^a	5 (1.7)	0 (0.0)

System Organ Class/Preferred Term	All Adverse Reactions (≥5% in POMALYST + Low-dose Dex arm, and at least 2% point higher than the High-dose-Dex arm)		Grade 3 or 4 (≥1% in POMALYST + Low-dose Dex arm, and at least 1% point higher than the High-dose-Dex arm)	
	POMALYST + Low-dose Dex (N=300)	High-dose Dex (N=150)	POMALYST + Low-dose Dex (N=300)	High-dose Dex (N=150)
Aspartate aminotransferase increased	4 (1.3) ^a	2 (1.3) ^a	3 (1.0)	0 (0.0)
Lymphocyte count decreased	3 (1.0) ^a	1 (0.7) ^a	3 (1.0)	0 (0.0)
Renal and urinary disorders				
Renal failure	31 (10.3) ^a	18 (12.0) ^a	19 (6.3)	8 (5.3)
Injury, poisoning and procedural complications				
Femur fracture ^b	5 (1.7) ^a	1 (0.7) ^a	5 (1.7)	1 (0.7)
Reproductive system and breast disorders				
Pelvic pain	6 (2.0) ^a	3 (2.0) ^a	4 (1.3)	0 (0.0)

^a Percentage did not meet the criteria to be considered as an adverse reaction for POMALYST for that category of event (i.e., all adverse events or Grade 3 or 4 adverse events).

^b Serious adverse reactions were reported in at least 3 patients in the POM + Low-dose Dex arm, AND at least 1% higher than the High-dose-Dex arm percentage.

Data cutoff: 01 March 2013

Other Adverse Reactions

Other adverse reactions of POMALYST in patients with multiple myeloma, not described above, and considered important:

Cardiac disorders: Myocardial infarction, Atrial fibrillation, Angina pectoris, Cardiac failure congestive

Ear and labyrinth disorders: Vertigo

Gastrointestinal disorders: Abdominal pain

General disorders and administration site conditions: General physical health deterioration, Non-cardiac chest pain, Multi-organ failure

Hepatobiliary disorders: Hyperbilirubinemia

Infections and infestations: Pneumocystis jiroveci pneumonia, Respiratory syncytial virus infection, Neutropenic sepsis, Bacteremia, Pneumonia respiratory syncytial viral, Cellulitis, Urosepsis, Septic shock, Clostridium difficile colitis, Pneumonia streptococcal, Lobar pneumonia, Viral infection, Lung infection

Investigations: Alanine aminotransferase increased, Hemoglobin decreased

Injury, poisoning and procedural complications: Fall, Compression fracture, Spinal compression fracture

Metabolism and nutritional disorders: Hyperkalemia, Failure to thrive

Nervous System disorders: Depressed level of consciousness, Syncope

Psychiatric disorders: Mental status change

Renal and urinary disorders: Urinary retention, Hyponatremia

Reproductive system and breast disorders: Pelvic pain

Respiratory, thoracic, and mediastinal disorders: Interstitial lung disease, Pulmonary embolism, Respiratory failure, Bronchospasm

Vascular disorders: Hypotension

6.2 Postmarketing Experience

The following adverse drug reactions have been identified from the worldwide postmarketing experience with POMALYST: Pancytopenia, tumor lysis syndrome, allergic reactions (e.g., angioedema, urticaria), elevated liver enzymes, hepatic failure (including fatal cases).

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp).

7.1 Drugs That May Increase Pomalidomide Plasma Concentrations

CYP1A2 inhibitors: Pomalidomide exposure is increased when POMALYST is co-administered with a strong CYP1A2 inhibitor (fluvoxamine) in the presence of a strong CYP3A4/5 and P-gp inhibitor (ketoconazole). Ketoconazole in the absence of a CYP1A2 inhibitor does not increase pomalidomide exposure. Avoid co-administration of strong CYP1A2 inhibitors (e.g. ciprofloxacin and fluvoxamine) [see *Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*]. If it is medically necessary to co-administer strong inhibitors of CYP1A2 in the presence of strong inhibitors of CYP3A4 and P-gp, POMALYST dose should be reduced by 50%.

The effect of a CYP1A2 inhibitor in the absence of a co-administered CYP3A4 and P-gp inhibitor has not been studied. Monitor for toxicities if CYP1A2 inhibitors are to be co-administered in the absence of a co-administered CYP3A4 and P-gp inhibitor, and reduce dose if needed.

7.2 Drugs That May Decrease Pomalidomide Plasma Concentrations

Smoking: Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

CYP1A2 inducers: Co-administration of POMALYST with drugs that are CYP1A2 inducers has not been studied and may reduce pomalidomide exposure.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [see *Boxed Warnings and Contraindications (4)*]

Risk Summary

POMALYST can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. POMALYST is a thalidomide analogue.

Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasticity of the bones, absence of bones, external ear abnormalities (including anotia, micropinna, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been documented, and mortality at or shortly after birth has been reported in about 40% of infants.

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

Animal Data

Pomalidomide was teratogenic in both rats and rabbits in the embryo-fetal developmental studies when administered during the period of organogenesis.

In rats, pomalidomide was administered orally to pregnant animals at doses of 25 to 1000 mg/kg/day. Malformations or absence of urinary bladder, absence of thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (vertebral, central, and/or neural arches) were observed at all dose levels. There was no maternal toxicity observed in this study. The lowest dose in rats resulted in an exposure (AUC) approximately 85-fold of the human exposure at the recommended dose of 4 mg/day. Other embryo-fetal toxicities included increased resorptions leading to decreased number of viable fetuses.

In rabbits, pomalidomide was administered orally to pregnant animals at doses of 10 to 250 mg/kg/day. Increased cardiac malformations such as interventricular septal defect were seen at all doses with significant increases at 250 mg/kg/day. Additional malformations observed at 250 mg/kg/day included anomalies in limbs (flexed and/or rotated fore- and/or hindlimbs, unattached or absent digit) and associated skeletal malformations (not ossified metacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent tibia), moderate dilation of the lateral ventricle in the brain, abnormal placement of the right subclavian artery, absent intermediate lobe in the lungs, low-set kidney, altered liver morphology, incompletely or not ossified pelvis, an increased average for supernumerary thoracic ribs, and a reduced average for ossified tarsals. No maternal toxicity was observed at the low dose (10 mg/kg/day) that resulted in cardiac anomalies in fetuses; this dose resulted in an exposure (AUC) approximately equal to that reported in humans at the recommended dose of 4 mg/day. Additional embryo-fetal toxicity included increased resorption.

8.3 Nursing Mothers

It is not known if pomalidomide is excreted in human milk. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from POMALYST, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of POMALYST in patients below the age of 18 years have not been established.

8.5 Geriatric Use

No dosage adjustment is required for POMALYST based on age.

Of the total number of patients in clinical studies of POMALYST, 44% were aged older than 65 years, while 10% were aged older than 75 years. No overall differences in effectiveness were observed between these patients and younger patients. In these studies, patients older than 65 years were more likely than patients less than or equal to 65 years of age to experience pneumonia.

8.6 Females of Reproductive Potential and Males

POMALYST can cause fetal harm when administered during pregnancy [see *Use in Specific Populations (8.1)*]. Females of reproductive potential must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy.

Females

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously: one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner’s vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALYST therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating POMALYST. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing POMALYST. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. POMALYST treatment must be discontinued during this evaluation.

Males

Pomalidomide is present in the semen of males who take POMALYST. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm.

8.7 Renal Impairment

Pomalidomide and its metabolites are primarily excreted by the kidneys [see *Clinical Pharmacology (12.3)*]. The influence of renal impairment on the safety, efficacy, and

pharmacokinetics of pomalidomide has not been evaluated. Patients with serum creatinine greater than 3.0 mg/dL were excluded in clinical studies. Avoid POMALYST in patients with a serum creatinine greater than 3.0 mg/dL.

8.8 Hepatic Impairment

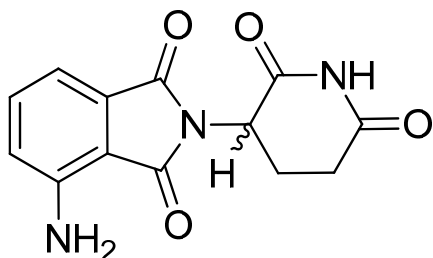
Pomalidomide is metabolized in the liver [see *Clinical Pharmacology (12.3)*]. The influence of hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x upper limit normal (ULN) were excluded in clinical studies. Avoid POMALYST in patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x ULN.

10 OVERDOSAGE

No specific information is available on the treatment of overdose with pomalidomide, and it is unknown whether pomalidomide or its metabolites are dialyzable.

11 DESCRIPTION

POMALYST is an immunomodulatory antineoplastic agent. The chemical name is (RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione and it has the following chemical structure:



The empirical formula for pomalidomide is $C_{13}H_{11}N_3O_4$ and the gram molecular weight is 273.24.

Pomalidomide is a yellow solid powder. It has limited to low solubility into organic solvents and it has low solubility in all pH solutions (about 0.01 mg/mL). Pomalidomide has a chiral carbon atom which exists as a racemic mixture of the R(+) and S(-) enantiomers.

POMALYST is available in 1-mg, 2-mg, 3-mg, and 4-mg capsules for oral administration. Each capsule contains pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pregelatinized starch, and sodium stearyl fumarate. The 1-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink. The 2-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink. The 3-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink. The 4-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF- α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the in vitro umbilical cord model.

12.2 Pharmacodynamics

The QTc prolongation potential of pomalidomide was evaluated in a single center, randomized, double-blind crossover study (N=72) using 4 mg pomalidomide, 20 mg pomalidomide, placebo, and 400 mg moxifloxacin (positive control). No significant QTc prolongation effect of pomalidomide was observed following pomalidomide doses of 4 and 20 mg.

12.3 Pharmacokinetics

Absorption

Following administration of single oral doses of POMALYST, the maximum plasma concentration (C_{max}) for pomalidomide occurs at 2 and 3 hours postdose. The systemic exposure (AUC) of pomalidomide increases in an approximately dose proportional manner.

In patients with multiple myeloma who received POMALYST 4 mg daily alone or in combination with dexamethasone, pomalidomide steady-state drug exposure was characterized by AUC(T) of 400 ng-h/mL and C_{max} of 75 ng/mL. Following multiple doses, pomalidomide has an accumulation ratio of 27% to 31%.

Distribution

Pomalidomide has a mean apparent volume of distribution (V_d/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours postdose ($\sim T_{max}$) after 4 days of once-daily dosing at 2 mg. Human plasma protein binding ranges from 12% to 44% and is not concentration dependent. Pomalidomide is a substrate for P-glycoprotein (P-gp).

Metabolism

Pomalidomide is primarily metabolized in the liver by CYP1A2 and CYP3A4. In vitro, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6.

Elimination

Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with multiple myeloma. Pomalidomide has a mean total body clearance (CL/F) of 7-10 L/h.

Following a single oral administration of [14 C]-pomalidomide (2 mg) to healthy subjects, approximately 73% and 15% of the radioactive dose was eliminated in urine and feces, respectively, with approximately 2% and 8% of the radiolabeled dose eliminated unchanged as pomalidomide in urine and feces.

Drug Interactions

Drugs that Inhibit Pomalidomide Metabolism

CYP1A2 Inhibitors: The effect of CYP1A2 inhibitors, in the absence of a co-administered CYP3A4 and P-gp inhibitor, is unknown. However, co-administration of fluvoxamine (a strong CYP1A2 inhibitor) in the presence of ketoconazole (a strong CYP3A4 and P-gp inhibitor) to 12 healthy male subjects increased exposure (geometric mean AUC_{INF}) to pomalidomide by 146% compared to pomalidomide administered alone [see *Dosage and Administration (2.2) and Drug Interactions (7.1)*].

Strong CYP3A4 and P-glycoprotein (P-gp) Inhibitors: Co-administration of ketoconazole (a strong CYP3A4 and P-gp inhibitor) in 16 healthy male subjects resulted in an increased exposure (geometric mean AUC_{INF}) to pomalidomide of 19% compared to pomalidomide administered alone.

Drugs that Induce Pomalidomide Metabolism

Strong CYP1A2 Inducers: Co-administration of POMALYST with drugs that are CYP1A2 inducers has not been studied and may reduce pomalidomide exposure.

Strong CYP3A4 Inducers: Co-administration of carbamazepine to 16 healthy male subjects decreased exposure (geometric mean AUC_{INF}) to pomalidomide by 21% compared to pomalidomide administered alone.

Dexamethasone: Co-administration of multiple doses of 4 mg POMALYST with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of CYP3A4) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.

In Vitro Inhibition of Drug Metabolizing Enzymes and Transporters by Pomalidomide

Pomalidomide does not inhibit or induce CYP450 enzymes or transporters in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of 12 monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of the exposure in patients at the recommended dose of 4 mg/day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study.

Pomalidomide was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames test), the in vitro assay using human peripheral blood lymphocytes, and the micronucleus test in orally treated rats administered doses up to 2000 mg/kg/day.

In a fertility and early embryonic development study in rats, drug-treated males were mated with untreated or treated females. Pomalidomide was administered to males and females at doses of 25 to 1000 mg/kg/day. When treated males were mated with treated females, there was an increase in post-implantation loss and a decrease in mean number of viable embryos at all dose levels. There were no other effects on reproductive functions or the number of pregnancies. The

lowest dose tested in animals resulted in an exposure (AUC) approximately 100-fold of the exposure in patients at the recommended dose of 4 mg/day. When treated males in this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

14 CLINICAL STUDIES

14.1 Multiple Myeloma

Trial 1 was a phase 2, multicenter, randomized open-label study in patients with relapsed multiple myeloma who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib. Patients were considered relapsed if they had achieved at least stable disease for at least 1 cycle of treatment to at least 1 prior regimen and then developed progressive disease. Patients were considered refractory if they experienced disease progression on or within 60 days of their last therapy. A total of 221 patients were randomized to receive POMALYST alone or POMALYST with Low-dose Dex. In Trial 1, the safety and efficacy of POMALYST 4 mg, once daily for 21 of 28 days, until disease progression, were evaluated alone and in combination with Low-dose Dex (40 mg/day given only on Days 1, 8, 15, and 22 of each 28-day cycle for patients aged 75 years or younger, or 20 mg/day given only on Days 1, 8, 15, and 22 of each 28-day cycle for patients aged greater than 75 years). Patients in the POMALYST alone arm were allowed to add Low-dose Dex upon disease progression.

Table 4 summarizes the baseline patient and disease characteristics in Trial 1. The baseline demographics and disease characteristics were balanced and comparable between the study arms.

Table 4: Baseline Demographic and Disease-Related Characteristics – Trial 1

	POMALYST (n=108)	POMALYST + Low-dose Dex (n=113)
Patient Characteristics		
Median age, years (range)	61 (37-88)	64 (34-88)
Age distribution, n (%)		
<65 years	65 (60.2)	60 (53.1)
≥65 years	43 (39.8)	53 (46.9)
Sex, n (%)		
Male	57 (52.8)	62 (54.9)
Female	51 (47.2)	51 (45.1)
Race/ethnicity, n (%)		
White	86 (79.6)	92 (81.4)
Black or African American	16 (14.8)	17 (15)
All other race	6 (5.6)	4 (3.6)
ECOG Performance, n (%)		
Status 0-1	95 (87.9)	100 (88.5)
Disease Characteristics		
Number of prior therapies		
Median (min, max)	5 (2, 12)	5 (2, 13)
Prior transplant, n (%)	82 (75.9)	84 (74.3)
Refractory to bortezomib and lenalidomide, n (%)	64 (59.3)	69 (61.1)

Data cutoff: 01 April 2011

Table 5 summarizes the analysis results of overall response rate (ORR) and duration of response (DOR), based on assessments by the Independent Review Adjudication Committee for the treatment arms in Trial 1. ORR did not differ based on type of prior antineoplastic therapy.

Table 5: Trial 1 Results

	POMALYST^a (n=108)	POMALYST + Low-dose Dex (n=113)
Response		
Overall Response Rate (ORR), ^b n (%)	8 (7.4)	33 (29.2)
95% CI for ORR (%)	(3.3, 14.1)	(21.0, 38.5)
Complete Response (CR), n (%)	0 (0.0)	1 (0.9)
Partial Response (PR), n (%)	8 (7.4)	32 (28.3)
Duration of Response (DOR)		
Median, months	NE	7.4
95% CI for DOR (months)	NE	(5.1, 9.2)

^a Results are prior to the addition of dexamethasone.

^b ORR = PR + CR per EBMT criteria.

CI, confidence interval; NE, not established (the median has not yet been reached).

Data cutoff: 01 April 2011

Trial 2 was a Phase 3 multi-center, randomized, open-label study, where POMALYST + Low-dose Dex therapy was compared to High-dose Dex in adult patients with relapsed and refractory multiple myeloma, who had received at least two prior treatment regimens, including lenalidomide and bortezomib, and demonstrated disease progression on or within 60 days of the last therapy. Patients with creatinine clearance \geq 45mL/min qualified for the trial. A total of 455 patients were enrolled in the trial: 302 in the POMALYST + Low-dose Dex arm and 153 in the High-dose Dex arm. Patients in the POMALYST + Low-dose Dex arm were administered 4 mg POMALYST orally on Days 1 to 21 of each 28-day cycle. Dexamethasone (40 mg) was administered once per day on Days 1, 8, 15 and 22 of a 28-day cycle. Patients > 75 years of age started treatment with 20 mg dexamethasone using the same schedule. For the High-dose Dex arm, dexamethasone (40 mg) was administered once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. Patients > 75 years of age started treatment with 20 mg dexamethasone using the same schedule. Treatment continued until patients had disease progression.

Baseline patient and disease characteristics were balanced and comparable between the study arms, as summarized in Table 6. Overall, 94% of patients had disease refractory to lenalidomide, 79% had disease refractory to bortezomib and 74% had disease refractory to both lenalidomide and bortezomib.

Table 6: Baseline Demographic and Disease-Related Characteristics – Trial 2

	POMALYST + Low-dose Dex (N=302)	High-dose Dex (N=153)
Patient Characteristics		
Median Age, years (range)	64 (35, 84)	65 (35, 87)
Age Distribution n (%)		
< 65 years	158 (52)	74 (48)
\geq 65 years	144 (48)	79 (52)
Sex n (%)		
Male	181 (60)	87 (57)
Female	121 (40)	66 (43)
Race/Ethnicity n (%)		
White	244 (81)	113 (74)
Black or African American	4 (1)	3 (2)
Asian	4 (1)	0 (0)
Other Race	2 (1)	2 (1)
Not Collected	48 (16)	35 (23)

ECOG Performance n (%)		
Status 0	110 (36)	36 (24)
Status 1	138 (46)	86 (56)
Status 2	52 (17)	25 (16)
Status 3	0 (0)	3 (2)
Missing	2 (1)	3 (2)
Disease Characteristics		
Number of Prior Therapies Median, (Min, Max)	5 (2, 14)	5 (2, 17)
Prior stem cell transplant n (%)	214 (71)	105 (69)
Refractory to bortezomib and lenalidomide n (%)	225 (75)	113 (74)

Data cutoff: 01 March 2013

Table 7 summarizes the progression free survival (PFS) and overall response rate (ORR) based on the assessment by the Independent Review Adjudication Committee (IRAC) review at the final PFS analysis and overall survival (OS) at the OS analysis. PFS was significantly longer with POMALYST + Low-dose Dex than High-dose Dex: HR 0.45 (95% CI: 0.35-0.59 p < 0.001). OS was also significantly longer with POMALYST + Low-dose Dex than High-dose Dex: HR 0.70 (95% CI: 0.54-0.92 p = 0.009). The Kaplan-Meier curves for PFS and OS for the ITT population are provided in Figures 1 and 2, respectively.

Table 7: Trial 2 Results

	POMALYST + Low-dose Dex (N=302)	High-dose Dex (N=153)
Progression Free Survival Time		
Number (%) of events	164 (54.3)	103 (67.3)
Median ^a (2-sided 95% CI) (months)	3.6 [3.0, 4.6]	1.8 [1.6, 2.1]
Hazard Ratio (Pom+LD-Dex:HD-Dex) 2-Sided 95% CI ^b	0.45 [0.35, 0.59]	
Log-Rank Test 2-sided P-Value ^c	<0.001	
Overall Survival Time^d		
Number (%) of deaths	147 (48.7)	86 (56.2)
Median ^a (2-sided 95% CI) (months)	12.4 [10.4, 15.3]	8.0 [6.9, 9.0]
Hazard Ratio (Pom+LD-Dex:HD-Dex) 2-Sided 95% CI ^e	0.70 [0.54, 0.92]	
Log-Rank Test 2-sided P-Value ^{f, g}	0.009	
Overall Response Rate, n (%)		
Complete Response	71 (23.5)	6 (3.9)
Very Good Partial Response	1 (0.3)	0
Partial Response	8 (2.6)	1 (0.7)
	62 (20.5)	5 (3.3)

Note: CI=Confidence interval; HD-Dex=High dose dexamethasone; IRAC=Independent Review Adjudication Committee; LD-Dex=Low dose dexamethasone.

^a The median is based on Kaplan-Meier estimate.

^b Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by age (≤ 75 vs > 75), diseases population (refractory to both Lenalidomide and Bortezomib vs not refractory to both drugs), and prior number of antimyeloma therapy ($= 2$ vs > 2), stratification factors for the trial.

^c The p-value is based on a stratified log-rank test with the same stratification factors as the above Cox model.

^d 53% of patients in the High-dose Dex arm subsequently received POMALYST.

^e Based on Cox proportional hazards model (unstratified) comparing the hazard functions associated with treatment groups.

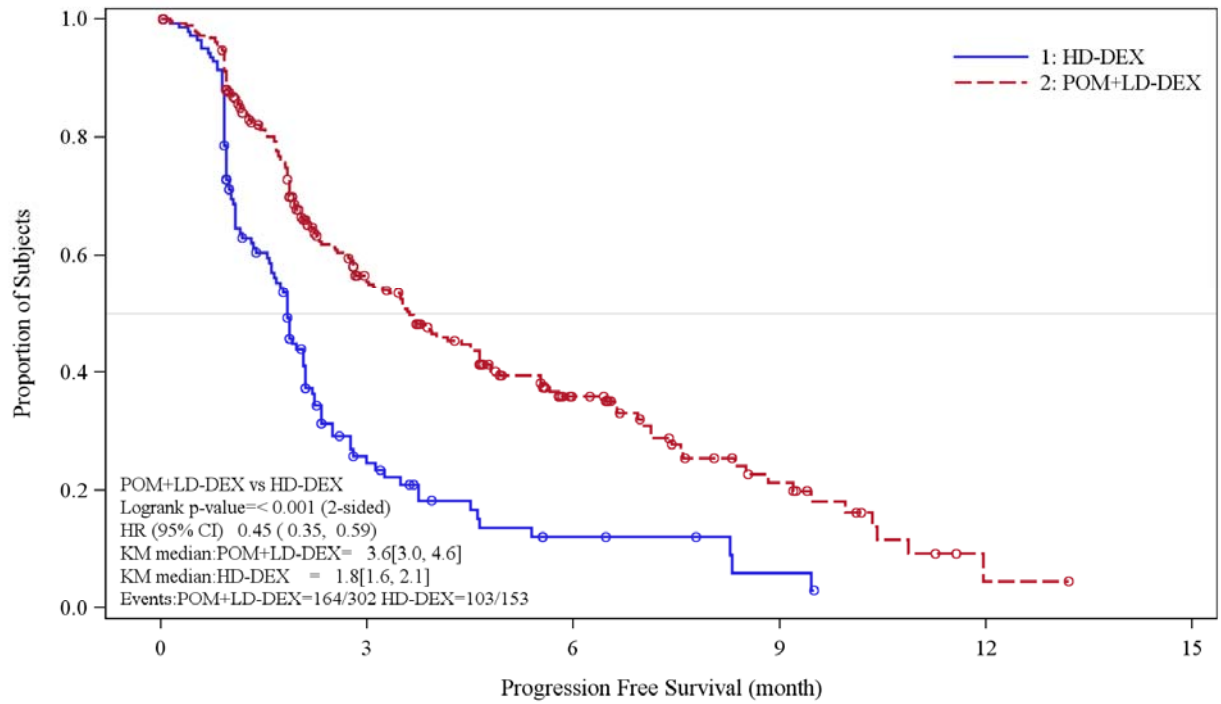
^f The p-value is based on an unstratified log-rank test.

^g Alpha control for PFS and OS.

Data cutoff: 07 Sep 2012 for PFS

Data cutoff: 01 Mar 2013 for OS and ORR

Figure 1: Progression Free Survival Based on IRAC Review of Response by IMWG Criteria (Stratified Log Rank Test) (ITT Population)

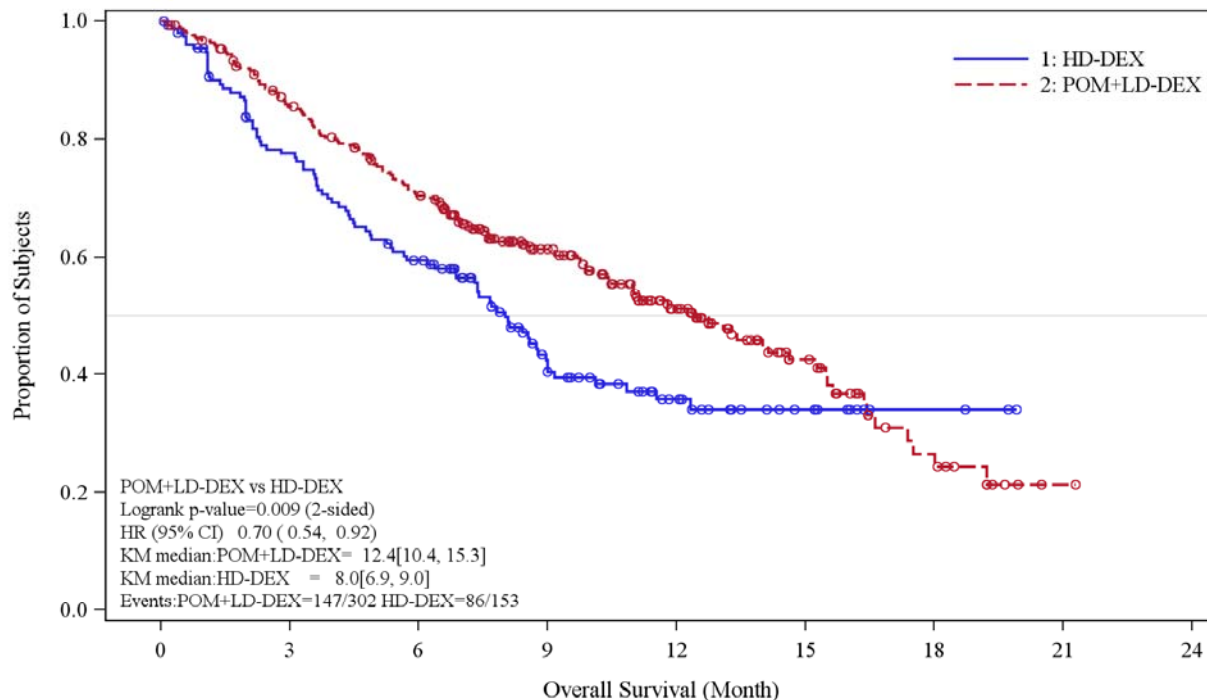


Number of subjects at risk:

1	153	21	6	2	0	
2	302	107	43	15	1	0

Data cut-off: 07 Sep 2012

Figure 2: Kaplan-Meier Curve of Overall Survival (ITT Population)



Number of subjects at risk:

1	153	112	84	44	24	11	3	0	
2	302	248	199	126	71	32	12	1	0

Data cutoff: 01 Mar 2013

15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. [Accessed on 29 January 2013, from <http://www.osha.gov/SLTC/hazardousdrugs/index.html>]

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Dark blue opaque cap and yellow opaque body, imprinted “POML” on the cap in white ink and “1 mg” on the body in black ink

- 1 mg bottles of 21 (NDC 59572-501-21)
- 1 mg bottles of 100 (NDC 59572-501-00)

Dark blue opaque cap and orange opaque body, imprinted “POML” on the cap and “2 mg” on the body in white ink

- 2 mg bottles of 21 (NDC 59572-502-21)
- 2 mg bottles of 100 (NDC 59572-502-00)

Dark blue opaque cap and green opaque body, imprinted “POML” on the cap and “3 mg” on the body in white ink

- 3 mg bottles of 21 (NDC 59572-503-21)
- 3 mg bottles of 100 (NDC 59572-503-00)

Dark blue opaque cap and blue opaque body, imprinted “POML” on the cap and “4 mg” on the body in white ink

4 mg bottles of 21 (NDC 59572-504-21)

4 mg bottles of 100 (NDC 59572-504-00)

16.2 Storage

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F). [See USP Controlled Room Temperature].

16.3 Handling and Disposal

Care should be exercised in handling of POMALYST. POMALYST capsules should not be opened or crushed. If powder from POMALYST contacts the skin, wash the skin immediately and thoroughly with soap and water. If POMALYST contacts the mucous membranes, flush thoroughly with water.

Follow procedures for proper handling and disposal of anticancer drugs. ¹

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling (*Medication Guide*)

Embryo-Fetal Toxicity

Advise patients that POMALYST is contraindicated in pregnancy [see *Contraindications (4)*]. POMALYST is a thalidomide analogue and may cause serious birth defects or death to a developing baby [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.1)*].

- Advise females of reproductive potential that they must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy.
- Initiate POMALYST treatment in females of reproductive potential only following a negative pregnancy test.
- Advise females of reproductive potential of the importance of monthly pregnancy tests and the need to use 2 different forms of contraception, including at least 1 highly effective form, simultaneously during POMALYST therapy, during therapy interruption, and for 4 weeks after she has completely finished taking POMALYST. Highly effective forms of contraception other than tubal ligation include IUD and hormonal (birth control pills, injections, patch, or implants) and a partner’s vasectomy. Additional effective contraceptive methods include latex or synthetic condom, diaphragm, and cervical cap.
- Instruct patient to immediately stop taking POMALYST and contact her doctor if she becomes pregnant while taking this drug, if she misses her menstrual period or experiences unusual menstrual bleeding, if she stops taking birth control, or if she thinks FOR ANY REASON that she may be pregnant.
- Advise patient that if her doctor is not available, she can call 1-888-668-2528 for information on emergency contraception [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*].
- Advise males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy.
- Advise male patients taking POMALYST that they must not donate sperm [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*].

- All patients must be instructed to not donate blood while taking POMALYST and for 1 month following discontinuation of POMALYST [see *Warnings and Precautions (5.1)* and *Use in Specific Populations (8.6)*].

POMALYST REMS Program

Because of the risk of embryo-fetal toxicity, POMALYST is only available through a restricted program called POMALYST REMS [see *Warnings and Precautions (5.2)*].

- Patients must sign a Patient-Physician Agreement Form and comply with the requirements to receive POMALYST. In particular, females of reproductive potential must comply with the pregnancy testing, contraception requirements, and participate in monthly telephone surveys. Males must comply with the contraception requirements [see *Use in Specific Populations (8.6)*].
- POMALYST is available only from pharmacies that are certified in POMALYST REMS. Provide patients with the telephone number and Web site for information on how to obtain the product.

Venous and Arterial Thromboembolism

Inform patients of the risk of developing DVT, PE, MI, and stroke and to report immediately any signs and symptoms suggestive of these events for evaluation [see *Boxed Warnings and Warnings and Precautions (5.3)*].

Hematologic Toxicities

Inform patients on the risks of developing neutropenia, thrombocytopenia, and anemia and the need to report signs and symptoms associated with these events to their healthcare provider for further evaluation [see *Warnings and Precautions (5.4)*].

Hepatotoxicity

Inform patients on the risks of developing hepatotoxicity, including hepatic failure and death, and to report signs and symptoms associated with these events to their healthcare provider for evaluation [see *Warnings and Precautions (5.5)*].

Hypersensitivity

Inform patients of the risk for angioedema and severe skin reactions and to report any signs and symptoms associated with these events to their healthcare provider for evaluation [see *Warnings and Precautions (5.6)*].

Dizziness and Confusional State

Inform patients of the potential risk of dizziness and confusional state with the drug, to avoid situations where dizziness or confusional state may be a problem, and not to take other medications that may cause dizziness or confusional state without adequate medical advice [see *Warnings and Precautions (5.7)*].

Neuropathy

Inform patients of the risk of neuropathy and to report the signs and symptoms associated with these events to their healthcare provider for further evaluation [see *Warnings and Precautions* (5.8)].

Second Primary Malignancies

Inform the patient that the potential risk of developing acute myelogenous leukemia during treatment with POMALYST is unknown [see *Warnings and Precautions* (5.9)].

Tumor Lysis Syndrome

Inform patients of the potential risk of tumor lysis syndrome and to report any signs and symptoms associated with this event to their healthcare provider for evaluation [see *Warnings and Precautions* (5.10)].

Dosing Instructions

Inform patients on how to take POMALYST [see *Dosage and Administration* (2.1)]

- POMALYST should be taken once daily at about the same time each day.
- POMALYST should be taken without food (at least 2 hours before or 2 hours after a meal).
- The capsules should not be opened, broken, or chewed. POMALYST should be swallowed whole with water.
- Instruct patients that if they miss a dose of POMALYST, they may still take it up to 12 hours after the time they would normally take it. If more than 12 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take POMALYST at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

Other Information

Advise patients who smoke to stop because smoking may reduce the efficacy of pomalidomide [see *Drug Interactions* (7.2)].

Manufactured for: Celgene Corporation

Summit, NJ 07901

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MEDICATION GUIDE
POMALYST® (POM-uh-list)
(pomalidomide)
capsules

What is the most important information I should know about POMALYST?

- Before you begin taking POMALYST, you must read and agree to all of the instructions in the POMALYST REMS® program.
- POMALYST may cause serious side effects including:

Possible birth defects (deformed babies) or death of an unborn baby. Females who are pregnant or who plan to become pregnant must not take POMALYST.

POMALYST is similar to the medicine thalidomide (THALOMID). We know thalidomide can cause severe life-threatening birth defects. POMALYST has not been tested in pregnant women. POMALYST has harmed unborn animals in animal testing.

Females must not get pregnant:

- For at least 4 weeks before starting POMALYST
- While taking POMALYST
- During any breaks (interruptions) in your treatment with POMALYST
- For at least 4 weeks after stopping POMALYST

If you become pregnant while taking POMALYST, stop taking it right away and call your healthcare provider. If your healthcare provider is not available, you can call 1-888-668-2528 for medical information.

Healthcare providers and patients should report all cases of pregnancy to:

- FDA MedWatch at 1-800-FDA-1088, and
- Celgene Corporation at 1-888-423-5436

POMALYST can pass into human semen:

- Males, including those who have had a vasectomy, must use a latex or synthetic condom during any sexual contact with a pregnant female or a female that can become pregnant while taking POMALYST, during any breaks (interruptions) in your treatment with POMALYST, and for 4 weeks after stopping POMALYST
- Do not have unprotected sexual contact with a female who is or could become pregnant. Tell your healthcare provider if you do have unprotected sexual contact with a female who is or could become pregnant
- Do not donate sperm while taking POMALYST, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping POMALYST. If a female becomes pregnant with your sperm, the baby may be exposed to POMALYST and may be born with birth defects

Men, if your female partner becomes pregnant, you should call your healthcare provider right away.

- **Blood clots in your arteries, veins, and lungs, heart attack, and stroke can happen if you take POMALYST.** Most people who take POMALYST will also take a blood thinner medicine to help prevent blood clots.

Before taking POMALYST, tell your healthcare provider:

- o If you have had a blood clot in the past
- o If you have high blood pressure, smoke, or if you have been told you have a high level of fat in your blood (hyperlipidemia)
- o About all the medicines you take. Certain other medicines can also increase your risk for blood clots

Call your healthcare provider or get medical help right away if you get any of the following during treatment with POMALYST:

- o **Signs or symptoms of a blood clot in the lung, arm, or leg may include:** shortness of breath, chest pain, or arm or leg swelling
- o **Signs or symptoms of a heart attack may include:** chest pain that may spread to the arms, neck, jaw, back, or stomach area (abdomen), feeling sweaty, shortness of breath, feeling sick or vomiting
- o **Signs or symptoms of stroke may include:** sudden numbness or weakness, especially on one side of the body, severe headache or confusion, or problems with vision, speech, or balance

What is POMALYST?

POMALYST is a prescription medicine, taken along with the medicine dexamethasone, used to treat people with multiple myeloma who:

- Have received at least 2 prior medicines to treat multiple myeloma, including a type of medicine known as a proteasome inhibitor and lenalidomide, **and**
- Their disease has become worse during treatment or within 60 days of finishing the last treatment

It is not known if POMALYST is safe and effective in people under 18 years of age.

Who should not take POMALYST?

Do not take POMALYST if you are pregnant, plan to become pregnant, or become pregnant during treatment with POMALYST. **See “What is the most important information I should know about POMALYST?”**

What should I tell my healthcare provider before taking POMALYST?

Before you take POMALYST, tell your healthcare provider if you:

- Smoke cigarettes
- Have any other medical conditions

- Are breastfeeding. POMALYST must not be used by women who are breastfeeding. It is not known if POMALYST passes into your breast milk and can harm your baby

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. POMALYST and other medicines may affect each other, causing serious side effects. Talk with your healthcare provider before taking any new medicines.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist.

How should I take POMALYST?

Take POMALYST exactly as prescribed and follow all the instructions of the POMALYST REMS program.

Before prescribing POMALYST, your healthcare provider will:

- o Explain the POMALYST REMS program to you
- o Have you sign the Patient-Physician Agreement Form
- Swallow POMALYST capsules whole with water 1 time a day. **Do not break, chew, or open your capsules**
- Take POMALYST at about the same time each day
- **POMALYST should be taken without food**, at least 2 hours before or 2 hours after a meal
- Do not open the POMALYST capsules or handle them any more than needed. If you touch a broken POMALYST capsule or the medicine in the capsule, wash the area of your body right away with soap and water
- If you miss a dose of POMALYST and it has been less than 12 hours since your regular time, take it as soon as you remember. If it has been more than 12 hours, just skip your missed dose. Do **not** take 2 doses at the same time
- If you take too much POMALYST, call your healthcare provider right away

Females who can become pregnant:

- Will have pregnancy tests weekly for 4 weeks, then every 4 weeks if your menstrual cycle is regular, or every 2 weeks if your menstrual cycle is irregular.

If you miss your period or have unusual bleeding, you will need to have a pregnancy test and receive counseling

- Must agree to use 2 different forms of effective birth control at the same time, for at least 4 weeks before, while taking, during any breaks (interruptions) in your treatment, and for at least 4 weeks after stopping POMALYST

Males who take POMALYST, even those who have had a vasectomy, must agree to use a latex or synthetic condom during sexual contact with a pregnant female or a female who can become pregnant.

What should I avoid while taking POMALYST?

- See “What is the most important information I should know about POMALYST?”
- **Females: Do not get pregnant and do not breastfeed while taking POMALYST**
Males: Do not donate sperm
- **Do not share POMALYST with other people.** It may cause birth defects and other serious problems
- **Do not donate blood** while you take POMALYST, during any breaks (interruptions) in your treatment, and for 4 weeks after stopping POMALYST. If someone who is pregnant gets your donated blood, her baby may be exposed to POMALYST and may be born with birth defects
- You should not smoke cigarettes while taking POMALYST. Smoking cigarettes during treatment with POMALYST may affect how well POMALYST works
- POMALYST can cause dizziness and confusion. Avoid taking other medicines that may cause dizziness and confusion during treatment with POMALYST. Avoid situations that require you to be alert until you know how POMALYST affects you

What are the possible side effects of POMALYST?

POMALYST may cause serious side effects, including:

- See “What is the most important information I should know about POMALYST?”
- **Low white blood cells (neutropenia), low platelets (thrombocytopenia), and low red blood cells (anemia).** POMALYST may cause low white blood cells, low platelets, and low red blood cells. You may need a blood transfusion or certain medicines if your blood counts drop too low. Your blood counts should be checked weekly for the first 8 weeks of treatment and monthly thereafter
- **Severe liver problems, including liver failure and death.** Tell your healthcare provider right away if you develop any of the following symptoms of liver problems:
 - o Yellowing of your skin or the white part of your eyes (jaundice)
 - o Dark or brown (tea-colored) urine
 - o Pain on the upper right side of your stomach area (abdomen)
 - o Bleeding or bruising more easily than normal
 - o Feeling very tired

Your healthcare provider should do blood tests to check your liver function during your treatment with POMALYST.

- **Severe allergic reactions and severe skin reactions.** Severe allergic reactions and severe skin reactions can happen with **POMALYST**. Call your healthcare provider if you have any symptoms of a severe allergic reaction including: swelling of your lips, mouth, tongue, or throat; or if you develop trouble breathing; or if you develop a skin reaction during treatment with **POMALYST**
- **Nerve damage.** Stop taking POMALYST and call your healthcare provider if you develop symptoms of nerve damage including: numbness, tingling, pain, burning sensation in your hands, legs, or feet
- **Tumor lysis syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause kidney failure and the need for dialysis treatment, abnormal heart rhythm, seizure, and sometimes death. Your healthcare provider may do blood tests to check you for TLS

Your healthcare provider may tell you to stop taking POMALYST if you develop certain serious side effects during treatment.

The most common side effects of POMALYST include:

- tiredness and weakness
- constipation
- shortness of breath
- diarrhea
- fever
- back pain
- nausea

These are not all the possible side effects of POMALYST. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store POMALYST?

- Store POMALYST at room temperature between 68°F to 77°F (20°C to 25°C)
- Return any unused POMALYST to Celgene or your healthcare provider

Keep POMALYST and all medicines out of the reach of children.

General information about the safe and effective use of POMALYST

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. **Do not** take POMALYST for conditions for which it was not prescribed. **Do not** give POMALYST to other people, even if they have the same symptoms you have. It may harm them and may cause birth defects.

If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about POMALYST that is written for health professionals.

For more information, call 1-888-423-5436 or go to www.CelgeneRiskManagement.com.

What are the ingredients in POMALYST?

Active ingredient: pomalidomide

Inactive ingredients: mannitol, pregelatinized starch, and sodium stearyl fumarate.

The 1-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink, and black ink.

The 2-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3, and white ink.

The 3-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, and white ink.

The 4-mg capsule shell contains gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2, and white ink.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for: Celgene Corporation, Summit, NJ 07901

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