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 US Approval: 2013

WARNING: EMBRYO-FETAL TOXICITY and VENOUS 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 two reliable methods of contraception (5.1, 8.6).**

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

VENOUS THROMBOEMBOLISM

- **Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMALYST (5.3).**

----------INDICATIONS AND USAGE----------

POMALYST is a thalidomide analogue indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

----------DOSAGE AND ADMINISTRATION----------

4 mg per day taken orally on days 1-21 of repeated 28-day cycles until disease progression.

----------DOSAGE FORMS AND STRENGTHS----------

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).

----------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 1-800-332-1088 or www.fda.gov/medwatch.

----------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 02/2013

FULL PRESCRIBING INFORMATION CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: EMBRYO-FETAL TOXICITY and VENOUS 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 Thromboembolism

- **Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMALYST. Prophylactic anti-thrombotic measures were employed in the clinical trial. Consider prophylactic measures after assessing an individual patient's underlying risk factors *[see Warnings and Precautions (5.3)]*.**

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

POMALYST is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate *[see Clinical Studies (14.1)]*. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

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 may 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 Toxicity

Table 1: Dose Modification Instructions for POMALYST for Hematologic Toxicities

Toxicity	Dose Modification
Neutropenia • 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	Interrupt POMALYST treatment, follow CBC weekly. Resume POMALYST at 3 mg daily.
• For each subsequent drop < 500 per mcL • Return to more than or equal to 500 per mcL	Interrupt POMALYST treatment Resume POMALYST at 1 mg less than the previous dose
Thrombocytopenia • Platelets < 25,000 per mcL • Platelets return to > 50,000 per mcL	Interrupt POMALYST treatment, follow CBC weekly Resume POMALYST treatment at 3 mg daily
• For each subsequent drop < 25,000 per mcL • Return to more than or equal to 50,000 per mcL	Interrupt POMALYST treatment Resume POMALYST at 1 mg less than previous dose.

*Note: ANC = Absolute Neutrophil Count

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.

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

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 two 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-Prescriber 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 [celgeneriskmanagement.com] or by telephone at 1-888-423-5436.

5.3 Venous Thromboembolism

Patients receiving POMALYST have developed venous thromboembolic events (Venous Thromboembolism [VTEs]) reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or anti-thrombotic treatment; 81% used aspirin, 16% warfarin, 21% heparin, and 3% clopidogrel. The rate of deep vein thrombosis or pulmonary embolism was 3%. Consider anti-coagulation prophylaxis after an assessment of each patient's underlying risk factors.

5.4 Hematologic Toxicity

Neutropenia was the most frequently reported Grade 3/4 adverse event (AE), followed by anemia and thrombocytopenia. Neutropenia of any grade was reported in 50% of patients in the trial. The rate of Grade 3/4 neutropenia was 43%. The rate of febrile neutropenia was 3%.

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 Hypersensitivity Reactions
Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.

5.6 Dizziness and Confusional State
In the trial, 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced grade 3/4 dizziness, and 3% of patients experienced grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice.

5.7 Neuropathy
In the trial, 18% of patients experienced neuropathy, with approximately 9% of the patients experiencing peripheral neuropathy. There were no cases of grade 3 or higher neuropathy adverse reactions reported.

5.8 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.

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 Thromboembolism *[see Boxed Warnings, Warnings and Precautions (5.3)]*
- Hematologic Toxicity *[see Warnings and Precautions (5.4)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.5)]*
- Dizziness and Confusional State *[see Warnings and Precautions (5.6)]*
- Neuropathy *[see Warnings and Precautions (5.7)]*
- Risk of Second Primary Malignancies *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience in 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 to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trial 1, data were evaluated from 219 patients (safety population) who received treatment with POMALYST + Low Dose Dexamethasone (Low dose Dex) (112 patients) or POMALYST alone (107 patients). Median number of treatment cycles was 5. Sixty three percent of patients in the study had a dose interruption of either drug due to adverse reactions. Thirty seven percent of patients in the study had a dose reduction of either drug due to adverse reactions. The discontinuation rate due to treatment-related adverse reaction was 3%.

Tables 2, 3 and 4 summarize all treatment-emergent adverse reactions reported for POMALYST + Low dose Dex and POMALYST alone groups regardless of attribution of relatedness to pomalidomide. In the absence of a randomized comparator arm, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient's underlying disease.

Table 2: Adverse Reactions Reported in 10% of Patients in Any Treatment Arm

	Trial 1	
	POMALYST[a] (N = 107)	POMALYST + Low dose Dex (N=112)
System Organ Class/Preferred Term	**n (%)**	**n (%)**
Number(%) of Patients With at Least One Treatment Emergent Adverse Reaction	107 (100)	112 (100)
General disorders and administration site conditions		
Fatigue and asthenia	59 (55)	70 (63)
Pyrexia	20 (19)	34 (30)
Edema peripheral	25 (23)	18 (16)
Chills	10 (9)	12 (11)
Pain	6 (6)	5 (5)
Blood and lymphatic system disorders		
Neutropenia	56 (52)	53 (47)
Anemia	41 (38)	44 (39)
Thrombocytopenia	27 (25)	26 (23)
Leukopenia	12 (11)	20 (18)
Lymphopenia	4 (4)	17 (15)
Gastrointestinal disorders		
Constipation	38 (36)	39 (35)
Diarrhea	36 (34)	37 (33)
Nausea	38 (36)	25 (22)

	Trial 1	
	POMALYST[a] (N = 107)	POMALYST + Low dose Dex (N=112)
System Organ Class/Preferred Term	**n (%)**	**n (%)**
Vomiting	15 (14)	15 (13)
Infections and infestations		
Pneumonia	25 (23)	32 (29)
Upper respiratory tract infection	34 (32)	28 (25)
Urinary tract infection	8 (8)	18 (16)
Musculoskeletal and connective tissue disorders		
Back pain	34 (32)	34 (30)
Musculoskeletal chest pain	23 (22)	22 (20)
Muscle spasms	20 (19)	21 (19)
Arthralgia	17 (16)	17 (15)
Musculoskeletal pain	12 (11)	17 (15)
Pain in extremity	5 (5)	16 (14)
Muscular weakness	13 (12)	13 (12)
Bone pain	13 (12)	5 (5)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	36 (34)	50 (45)
Cough	15 (14)	23 (21)
Epistaxis	16 (15)	12 (11)
Metabolism and nutritional disorders		
Decreased appetite	23 (22)	20 (18)
Hyperglycemia	13 (12)	17 (15)
Hyponatremia	11 (10)	14 (13)
Hypercalcemia	22 (21)	13 (12)
Hypocalcemia	6 (6)	13 (12)
Hypokalemia	11 (10)	12 (11)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	6 (6)	18 (16)
Rash	23 (22)	18 (16)
Night sweats	5 (5)	14 (13)
Dry skin	10 (9)	12 (11)
Pruritus	16 (15)	12 (11)
Nervous system disorders		
Dizziness	21 (20)	19 (17)
Tremor	10 (9)	14 (13)
Headache	14 (13)	9 (8)
Neuropathy peripheral	11 (10)	8 (7)
Investigations		
Blood creatinine increased	16 (15)	12 (11)
Weight increased	1 (1)	12 (11)
Weight decreased	15 (14)	9 (8)
Psychiatric disorders		
Insomnia	7 (7)	16 (14)
Confusional state	11 (10)	15 (13)
Anxiety	12 (11)	8 (7)
Renal and urinary disorders		
Renal failure	16 (15)	11 (10)

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

Table 3: Grade 3/4 Adverse Reactions Reported in ≥ 5% of Patients in Any Treatment Arm

	Trial 1	
	POMALYST[a] (N = 107)	**POMALYST + Low dose Dex (N=112)**
System Organ Class/Preferred Term [a]	n (%)	n (%)
Number(%) of Patients With at Least One Treatment Emergent NCI CTC Grade 3 or 4 Adverse Reaction	96 (90)	99 (88)
Blood and lymphatic system disorders		
Neutropenia	50 (47)	43 (38)
Anemia	24 (22)	23 (21)
Thrombocytopenia	24 (22)	21 (19)
Leukopenia	6 (6)	11 (10)
Lymphopenia	2 (2)	8 (7)
Infections and infestations		
Pneumonia	17 (16)	26 (23)
Urinary tract infection	2 (2)	9 (8)
Sepsis	6 (6)	3 (3)
Metabolism and nutritional disorders		
Hypercalcemia	10 (9)	1 (1)
General disorders and administration site conditions		
Fatigue and asthenia	12 (11)	14 (13)
Investigations		
Blood creatinine increased	6 (6)	3 (3)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	7 (7)	14 (13)
Musculoskeletal and connective tissue disorders		
Back pain	13 (12)	10 (9)
Muscular weakness	6 (6)	4 (4)
Renal and urinary disorders		
Renal failure	10 (9)	7 (6)

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

Table 4: Serious Adverse Reactions Reported in 2 or more Patients

	Trial 1	
	POMALYST[a] (N = 107)	**POMALYST+ Low dose Dex (N=112)**
System Organ Class/Preferred Term	**n (%)**	**n (%)**
Number(%) of Patients With at Least One Treatment Emergent Serious Adverse Reaction	72 (67)	69 (62)
Infections and infestations		
Pneumonia	15 (14)	21 (19)
Urinary tract infection	0 (0)	6 (5)
Sepsis	6 (6)	3 (3)

Respiratory, Thoracic and mediastinal disorders		
Dyspnea	5 (5)	7 (6)
General disorders and administration site conditions		
Pyrexia	3 (3)	5 (5)
General physical health deterioration	0 (0)	2 (2)
Cardiac Disorders		
Atrial fibrillation	2 (2)	3 (3)
Cardiac failure congestive	0 (0)	3 (3)
Renal and urinary disorders		
Renal failure	9 (8)	7 (6)
Gastrointestinal disorders		
constipation	1 (1)	3 (3)
Blood and Lymphatic system disorders		
Febrile neutropenia	5 (5)	1 (1)
Metabolism and nutrition disorders		
Dehydration	5 (5)	3 (3)
Hypercalcemia	5 (5)	2 (2)
Musculoskeletal and connective tissue disorders		
Back pain	4 (4)	2 (2)

[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.

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

Ear and Labyrinth Disorders: Vertigo
Hepatobiliary Disorders: Hyperbilirubinemia
Infections and Infestations: Pneumocystis jiroveci pneumonia, Respiratory syncytial virus infection, Neutropenic sepsis
Investigations: Alanine aminotransferase increased
Metabolism and Nutritional Disorders: Hyperkalemia
Renal and Urinary Disorders: Urinary retention
Reproductive System and Breast Disorders: Pelvic Pain
Respiratory, Thoracic and Mediastinal Disorders: Interstitial Lung Disease

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with POMALYST. 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

CYP3A, CYP1A2 or P-gp inhibitors: Co-administration of POMALYST with drugs that are strong inhibitors of CYP1A2, CYP3A (e.g. ketoconazole) or P-gp could increase exposure and should be avoided.

7.2 Drugs That May Decrease Pomalidomide Plasma Concentrations

CYP3A, CYP1A2 or P-gp inducers: Co-administration of POMALYST with drugs that are strong inducers of CYP1A2, CYP3A (e.g. rifampin) or P-gp could decrease exposure and should be avoided.

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

Dexamethasone: Co-administration of multiple doses of 4 mg POMALYST with 20 mg to 40 mg dexamethasone (a weak inducer of CYP3A) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.

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 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Animal Data

Pomalidomide was teratogenic in both rats and rabbits in the embryofetal 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 per kg per day. Malformations of 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 per day. Other embryofetal 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 per kg per day. Increased cardiac malformations such as interventricular septal defect were seen at all doses with significant increases at 250 mg per kg per day. Additional malformations observed at 250 mg per kg per 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 per kg per 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 per day. Additional embryofetal 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 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, 41 percent were 65 and over, while 12 percent were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. In this study, patients greater than or equal to 65 years of age 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 two 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 one 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

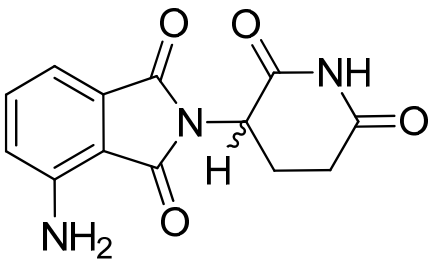
Pomalidomide is metabolized in the liver [*see Clinical Pharmacology (12.3)*]. The influence of hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x upper limit normal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

12.3 Pharmacokinetics

Absorption
Following administration of single oral doses of POMALYST, the Cmax for pomalidomide occurs at 2 and 3 hours post dose. 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.hr/ mL and maximum plasma concentration (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 (Vd/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 post-dose (~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.

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/ hr.

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-Drug Interactions
Pomalidomide does not inhibit or induce CYP450 enzymes or any of the 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 twelve 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/per 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 on 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 one cycle of treatment to at least one 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 per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients 75 years or younger, or 20mg per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients greater than 75 years of age). Patients in the POMALYST alone arm were allowed to add Low dose Dex upon disease progression.

Table 5 summarizes the baseline patient and disease characteristics in study Trial 1. The baseline demographics and disease characteristics were balanced and comparable between the study arms.

Table 5: 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 greater than or equal to 65 years	 65 (60.2) 43 (39.8)	 60 (53.1) 53 (46.9)
Sex n (%) Male Female	 57 (52.8) 51 (47.2)	 62 (54.9) 51 (45.1)
Race/Ethnicity n (%)		

White Black or African American All Other Race	86 (79.6) 16 (14.8) 6 (5.6)	92 (81.4) 17 (15) 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)

Table 6 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 Study 1. Overall response rate did not differ based on type of prior anti-myeloma therapy.

Table 6: Trial 1 Results

	POMALYST [2] **(N=108)**	**POMALYST/ Low dose Dex** **(N = 113)**
Response		
Overall Response Rate (ORR)[1], 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)

1. ORR =PR+CR per EBMT criteria,
2. Results are prior to the addition of dexamethasone

NE = not established (the median has not yet been reached), CI: confidence interval

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
1 mg bottles of 100

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
2 mg bottles of 100

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
3 mg bottles of 100

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
4 mg bottles of 100

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.

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published[1].

17 PATIENT COUNSELING INFORMATION

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

Embryo-Fetal Toxicity
Advise patients that POMALYST is contraindicated in pregnancy *[see Contraindicatons (4)]*. POMALYST is a thalidomide analog 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 two different forms of contraception including at least one 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 call POMALYST REMS *[see Warnings and Precautions (5.2)]*.

- Patients must sign a Patient-Prescriber 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 program. Provide patients with the telephone number and website for information on how to obtain the product

Venous Thromboembolism
Inform patients of the potential risk of developing venous thromboembolic events and discuss the need for appropriate prophylactic treatment.

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 health care provider for further evaluation.

Hypersensitivity
Inform patients of the potential for a severe hypersensitivity reaction to POMALYST if they have had such a reaction in the past to either THALOMID® or REVLIMID® .

Dizziness and Confusional State
Inform patients of the potential risk of dizziness and confusion with the drug and to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice.

Neuropathy
Inform patients of the risk of neuropathy and report the signs and symptoms associated with these events to their health care provider for further evaluation.

Second Primary Malignancies
Inform the patient that the potential risk of developing acute myelogenous leukemia during treatment with POMALYST is unknown.

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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