℞ POMALIDOMIDE
POMADEX 1/2/3/4
1mg/2mg/3mg/4mg Capsule
Immunosuppressant
2069504

℞

POMALIDOMIDE

POMADEX 1/2/3/4

1mg/2mg/3mg/4mg Capsule

Immunosuppressant

FORMULATION

Pomalidomide Capsule 1 mg:
Each capsule contains: Pomalidomide.....1 mg
Pomalidomide Capsule 2 mg :
Each capsule contains: Pomalidomide.....2 mg
Pomalidomide Capsule 3 mg:
Each capsule contains: Pomalidomide.....3 mg
Pomalidomide Capsule 4 mg:
Each capsule contains: Pomalidomide.....4 mg

Description:

Pomalidomide Capsule 1 mg:
Opaque, white cap and opaque white body, size '5' hard gelatin capsules imprinted with 'H' on cap and 'P1' on body, filled with pale yellow to yellowish color powder.

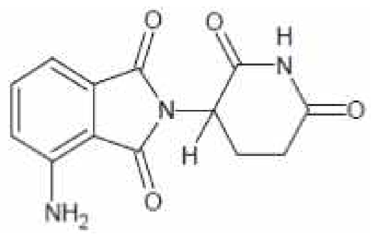
Pomalidomide Capsule 2 mg:
Opaque, white cap and opaque brown body, size '4' hard gelatin capsules imprinted with 'H' on cap and 'P2' on body, filled with pale yellow to yellowish color powder.

Pomalidomide Capsule 3 mg:
Opaque, white cap and opaque pink body, size '3' hard gelatin capsules imprinted with 'H' on cap and 'P3' on body, filled with pale yellow to yellowish color powder.

Pomalidomide Capsule 4 mg:
Opaque, white cap and opaque white body, size '2' hard gelatin capsules imprinted with 'H' on cap and 'P4' on body, filled with pale yellow to yellowish color powder.

DRUG DESCRIPTION

Pomalidomide is described chemically as (RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-1H-isoindoline-1,3-dione 3-amino-N-(2,6-dioxo-3-piperidyl)phthalamide 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline. The molecular formula is $C_{13}H_{11}N_3O_4$ and the molecular weight is 273.24 The chemical structure of Pomalidomide is:



Pomalidomide is a pale yellow to yellow color powder, and a pKa of 10.75. It is soluble in Dimethylformamide and in Dimethylsulfoxide.
Pomalidomide Capsule contain the following inactive ingredients: Pregelatinized starch (Starch 1500), Mannitol (Pearlitol SD 200), Microcrystalline Cellulose (AVICEL PH 101), Empty Hard Gelatin Capsule Shells.

THERAPEUTIC INDICATIONS

Multiple Myeloma

POMALIDOMIDE 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.

POSOLOGY AND METHOD OF ADMINISTRATION

Assessment Prior To Initiating Pomalidomide.

Multiple Myeloma

Females of reproductive potential must have negative pregnancy testing and use contraception methods before initiating POMALIDOMIDE [see WARNINGS AND PRECAUTIONS and Use In Specific Populations].
The recommended starting dose of POMALIDOMIDE is 4 mg once daily orally on Days 1-21 of repeated 28-day cycles until disease progression. POMALIDOMIDE should be given in combination with dexamethasone [see Clinical Studies].
POMALIDOMIDE may be taken with water. Inform patients not to break, chew, or open the capsules. POMALIDOMIDE may be taken with or without food.

Dose Adjustments For Toxicities

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

To initiate a new cycle of POMALIDOMIDE 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 POMALIDOMIDE.
Permanently discontinue POMALIDOMIDE for angioedema, skin exfoliation, bullae, or any other severe dermatologic reaction [see WARNINGS AND PRECAUTIONS].
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.

Dosage Adjustment For Strong CYP1A2 Inhibitors

Avoid concomitant use of POMALIDOMIDE with strong inhibitors of CYP1A2. Consider alternative treatments. If a strong CYP1A2 inhibitor must be used, reduce POMALIDOMIDE dose by 50% [see DRUG INTERACTIONS and CLINICAL PHARMACOLOGY].

Dosage Adjustment For Patients With Severe Renal Impairment On Hemodialysis

For patients with severe renal impairment requiring dialysis, the recommended starting dose is 3 mg daily (25% dose reduction). Take POMALIDOMIDE after completion of dialysis procedure on hemodialysis days. [see Use In Specific Populations and CLINICAL PHARMACOLOGY].

Dosage Adjustment For Patients With Hepatic Impairment

For patients with mild or moderate hepatic impairment (Child-Pugh classes A or B), the recommended starting dose is 3 mg daily (25% dose reduction). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose is 2 mg (50% dose reduction) [see Use In Specific Populations and CLINICAL PHARMACOLOGY].

CONTRAINDICATIONS

Pregnancy

POMALIDOMIDE can cause fetal harm when administered to a pregnant female [see WARNINGS AND PRECAUTIONS and Use In Specific Populations]. POMALIDOMIDE 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 risk to a fetus.

DRUG INTERACTIONS

Drugs That Affect Pomalidomide Plasma Concentrations

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A4. Pomalidomide is also a substrate for Pglycoprotein (P-gp).

CYP1A2 Inhibitors

In healthy volunteers, co-administration of fluvoxamine, a strong CYP1A2 inhibitor, increased Cmax and AUC of pomalidomide by 24% and 125% respectively [see CLINICAL PHARMACOLOGY]. Increased pomalidomide exposure increases the risk of exposure related toxicities.
Avoid co-administration of strong CYP1A2 inhibitors (e.g. ciprofloxacin and fluvoxamine) [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY]. If co-administration is unavoidable, reduce the POMALIDOMIDE dose [see DOSAGE AND ADMINISTRATION].

WARNINGS AND PRECAUTIONS

WARNINGS

Included as part of the "PRECAUTIONS" Section

PRECAUTIONS

Embryo-Fetal Toxicity

POMALIDOMIDE 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]. POMALIDOMIDE is only available through the POMALIDOMIDE REMS program [see POMALIDOMIDE REMS Program].

Females Of Reproductive Potential

Females of reproductive potential must avoid pregnancy while taking POMALIDOMIDE 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 POMALIDOMIDE during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALIDOMIDE 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 POMALIDOMIDE therapy and then weekly during the first month, then monthly thereafter in females with regular menstrual cycles, or every 2 weeks in females with irregular menstrual cycles [see Use In Specific Populations].

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 POMALIDOMIDE and for up to 4 weeks after discontinuing POMALIDOMIDE even if they have undergone a successful vasectomy. Male patients taking POMALIDOMIDE must not donate sperm [see Use In Specific Populations].
Blood Donation Patients must not donate blood during treatment with POMALIDOMIDE 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 POMALIDOMIDE.

POMALIDOMIDE REMS Program

Because of the embryo-fetal risk [see Embryo-Fetal Toxicity], POMALIDOMIDE is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called "POMALIDOMIDE REMS."

Required components of the POMALIDOMIDE REMS program include the following:

- Prescribers must be certified with the POMALIDOMIDE 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 [see Use In Specific Populations].
- Pharmacies must be certified with the POMALIDOMIDE REMS program, must only dispense to patients who are authorized to receive POMALIDOMIDE and comply with REMS requirements.

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 POMALIDOMIDE. In Trial 2, where anticoagulant therapies were mandated, thromboembolic events occurred in 8.0% of patients treated with POMALIDOMIDE 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 POMALIDOMIDE 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 POMALIDOMIDE 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.

Increased Mortality In Multiple Myeloma When Pembrolizumab Is Added To Dexamethasone And A Thalidomide Analogue

No PD-1 or PD-L1 blocking antibodies are approved for the treatment of multiple myeloma. In two randomized clinical trials in patients with multiple myeloma, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone resulted in increased mortality. In Study KN183 (NCT02576977), patients with relapsed or refractory multiple myeloma were randomized to receive pomalidomide and dexamethasone with (n = 125) or without (n = 124) pembrolizumab. The hazard ratio for overall survival (OS) was 1.61 (95% CI: 0.91, 2.85), increasing the relative risk of death by more than 50% in the experimental arm containing pembrolizumab. Causes of death in the experimental arm, excluding disease progression, included: myocarditis, Stevens- Johnson syndrome, myocardial infarction, pericardial hemorrhage, cardiac failure, respiratory tract infection, neutropenic sepsis, sepsis, multiple organ dysfunction, and respiratory failure. In Study KN185 (NCT02579863), patients with newly-diagnosed multiple myeloma were randomized to receive lenalidomide and dexamethasone with (n = 151) or without (n = 150) pembrolizumab. The hazard ratio for OS was 2.06 (95% CI: 0.93, 4.55), increasing the relative risk of death by more than 100% in the experimental arm containing pembrolizumab. Causes of death in the experimental arm, excluding disease progression, included: intestinal ischemia, cardio-respiratory arrest, suicide, pulmonary embolism, cardiac arrest, pneumonia, sudden death, myocarditis, large intestine perforation, and cardiac failure.
The addition of a PD-1 or PD-L1 blocking antibody to a thalidomide analogue is not recommended for the treatment of patients with multiple myeloma outside of controlled clinical trials.

Hematologic Toxicity

In trials 1 and 2 in patients who received POMALIDOMIDE + 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].

Hepatotoxicity

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

Hypersensitivity Reactions

Angioedema and severe dermatologic reactions have been reported. Discontinue POMALIDOMIDE for angioedema, skin exfoliation, bullae, or any other severe dermatologic reactions, and do not resume therapy [see DOSAGE AND ADMINISTRATION].

Dizziness And Confusional State

In trials 1 and 2 in patients who received POMALIDOMIDE + 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.

Neuropathy

In trials 1 and 2 in patients who received POMALIDOMIDE + 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.

Risk Of Second Primary Malignancies

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

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.

Embryo-Fetal Toxicity

Advise patients that POMALIDOMIDE is contraindicated in pregnancy [see CONTRAINDICATIONS]. POMALIDOMIDE is a thalidomide analogue and may cause serious birth defects or death to a developing baby [see WARNINGS AND PRECAUTIONS and Use In Specific Populations].

- Advise females of reproductive potential that they must avoid pregnancy while taking POMALIDOMIDE and for at least 4 weeks after completing therapy.
- Initiate POMALIDOMIDE 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 POMALIDOMIDE therapy, during therapy interruption, and for 4 weeks after she has completely finished taking POMALIDOMIDE. 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 POMALIDOMIDE and contact her healthcare provider 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 males to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALIDOMIDE and for up to 4 weeks after discontinuing POMALIDOMIDE even if they have undergone a successful vasectomy.
- Advise male patients taking POMALIDOMIDE that they must not donate sperm [see WARNINGS AND PRECAUTIONS and Use In Specific Populations].
- All patients must be instructed to not donate blood while taking POMALIDOMIDE and for 1 month following discontinuation of POMALIDOMIDE [see WARNINGS AND PRECAUTIONS].
  POMALIDOMIDE REMS Program
  Because of the risk of embryo-fetal toxicity, POMALIDOMIDE is only available through a restricted program called POMALIDOMIDE REMS [see WARNINGS AND PRECAUTIONS].
- Patients must sign a Patient-Physician Agreement Form and comply with the requirements to receive POMALIDOMIDE. 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].
- POMALIDOMIDE is available only from pharmacies that are certified in POMALIDOMIDE 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 WARNINGS AND PRECAUTIONS].

Increased Mortality In Multiple Myeloma Patients When Pembrolizumab Was Added To Dexamethasone And A Thalidomide Analogue Regimen

Inform patients of potential for increased risk of death in people with multiple myeloma when a PD-1 blocking antibody was added to a dexamethasone and thalidomide analogue treatment regimen [see WARNINGS AND PRECAUTIONS].

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].

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].

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].

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].

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].

Second Primary Malignancies

Inform the patient that the potential risk of developing acute myelogenous leukemia during treatment with POMALIDOMIDE is unknown [see WARNINGS AND PRECAUTIONS].

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].

Smoking Tobacco

Advise patients that smoking tobacco may reduce the efficacy of POMALIDOMIDE.

Dosing Instructions

Inform patients on how to take POMALIDOMIDE [see DOSAGE AND ADMINISTRATION]

- POMALIDOMIDE should be taken once daily at about the same time each day.
- Patients on hemodialysis should take POMALIDOMIDE following hemodialysis, on hemodialysis days.
- POMALIDOMIDE may be taken with or without food.
- The capsules should not be opened, broken, or chewed. POMALIDOMIDE should be swallowed whole with water.
- Instruct patients that if they miss a dose of POMALIDOMIDE 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 POMALIDOMIDE at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

Nonclinical Toxicology

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 100fold 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.

Use In Specific Populations

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to POMALIDOMIDE during pregnancy as well as female partners of male patients who are exposed to POMALIDOMIDE. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to POMALIDOMIDE to the FDA.

Risk Summary

Based on the mechanism of action [see CLINICAL PHARMACOLOGY] and findings from animal studies, POMALIDOMIDE can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy [see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS].
POMALIDOMIDE 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. Pomalidomide crossed the placenta after administration to pregnant rabbits [see Data]. 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 risk 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 POMALIDOMIDE to the FDA.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

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.
Following daily oral administration of pomalidomide from Gestation Day 7 through Gestation Day 20 in pregnant rabbits, fetal plasma pomalidomide concentrations were approximately 50% of the maternal Cmax at all dosages (5 to 250 mg/kg/day), indicating that pomalidomide crossed the placenta.

Lactation

Risk Summary

There is no information regarding the presence of pomalidomide in human milk, the effects of POMALIDOMIDE on the breastfed infant, or the effects of POMALIDOMIDE on milk production. Pomalidomide was excreted in the milk of lactating rats [see Data]. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from POMALIDOMIDE advise a nursing woman to discontinue breastfeeding during treatment with POMALIDOMIDE.

Data

Animal Data

Following a single oral administration of pomalidomide to lactating rats approximately 14 days postpartum, pomalidomide was transferred into milk, with milk to plasma ratios of 0.63 to 1.46.

Females And Males Of Reproductive Potential

Pregnancy Testing

POMALIDOMIDE can cause fetal harm when administered during pregnancy [see Pregnancy]. Verify the pregnancy status of females of reproductive potential prior to initiating POMALIDOMIDE therapy and for at least 4 weeks after completing therapy. Advise females of reproductive potential that they must avoid pregnancy while taking POMALIDOMIDE.
Females of reproductive potential must have 2 negative pregnancy tests before initiating POMALIDOMIDE. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing POMALIDOMIDE. 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. POMALIDOMIDE treatment must be discontinued during this evaluation.

Contraception

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 POMALIDOMIDE during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALIDOMIDE 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.

Males

Pomalidomide is present in the semen of males who take POMALIDOMIDE. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALIDOMIDE and for up to 4 weeks after discontinuing POMALIDOMIDE even if they have undergone a successful vasectomy. Male patients taking POMALIDOMIDE must not donate sperm.

Infertility

Based on findings in animals, female fertility may be compromised by treatment with POMALIDOMIDE [see Nonclinical Toxicology].

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

No dosage adjustment is required for POMALIDOMIDE based on age.
Of the total number of patients in clinical studies of POMALIDOMIDE 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.

Renal Impairment

In patients with severe renal impairment requiring dialysis, the AUC of pomalidomide increased by 38% and the rate of SAE increased by 64% relative to patients with normal renal function; therefore, starting dose adjustment is recommended. For patients with severe renal impairment requiring dialysis, POMALIDOMIDE should be administered after the completion of hemodialysis on dialysis days because exposure of pomalidomide could be significantly decreased during dialysis [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].

Hepatic Impairment

Pomalidomide is metabolized primarily by the liver. Following single dose administration, the AUC of pomalidomide increased 51%, 58%, and 72% in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. Dose adjustment is recommended in patients with hepatic impairment [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].

Smoking Tobacco

Cigarette smoking reduces pomalidomide AUC by 32% due to CYP1A2 induction. Advise patients that smoking may reduce the efficacy of pomalidomide [see CLINICAL PHARMACOLOGY].

PREGNANCY AND LACTATION

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in females exposed to POMALIDOMIDE during pregnancy as well as female partners of male patients who are exposed to POMALIDOMIDE. This registry is also used to understand the root cause for the pregnancy. Report any suspected fetal exposure to POMALIDOMIDE to the FDA.

Risk Summary

Based on the mechanism of action [see CLINICAL PHARMACOLOGY] and findings from animal studies, POMALIDOMIDE can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy [see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS].
POMALIDOMIDE 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. Pomalidomide crossed the placenta after administration to pregnant rabbits [see Data]. 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 risk 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.
The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

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.

Following daily oral administration of pomalidomide from Gestation Day 7 through Gestation Day 20 in pregnant rabbits, fetal plasma pomalidomide concentrations were approximately 50% of the maternal Cmax at all dosages (5 to 250 mg/kg/day), indicating that pomalidomide crossed the placenta.

Lactation

Risk Summary

There is no information regarding the presence of pomalidomide in human milk, the effects of POMALIDOMIDE on the breastfed infant, or the effects of POMALIDOMIDE on milk production. Pomalidomide was excreted in the milk of lactating rats [see Data]. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed infants from POMALIDOMIDE advise a nursing woman to discontinue breastfeeding during treatment with POMALIDOMIDE.

Data

Animal Data

Following a single oral administration of pomalidomide to lactating rats approximately 14 days postpartum, pomalidomide was transferred into milk, with milk to plasma ratios of 0.63 to 1.46.

Females And Males Of Reproductive Potential

Pregnancy Testing

POMALIDOMIDE can cause fetal harm when administered during pregnancy [see Pregnancy]. Verify the pregnancy status of females of reproductive potential prior to initiating POMALIDOMIDE therapy and for at least 4 weeks after completing therapy. Advise females of reproductive potential that they must avoid pregnancy while taking POMALIDOMIDE.
Females of reproductive potential must have 2 negative pregnancy tests before initiating POMALIDOMIDE. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing POMALIDOMIDE. 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. POMALIDOMIDE treatment must be discontinued during this evaluation.

Contraception

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 POMALIDOMIDE during therapy, during dose interruptions, and continuing for 4 weeks following discontinuation of POMALIDOMIDE 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.

Males

Pomalidomide is present in the semen of males who take POMALIDOMIDE. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking POMALIDOMIDE and for up to 4 weeks after discontinuing POMALIDOMIDE even if they have undergone a successful vasectomy. Male patients taking POMALIDOMIDE must not donate sperm.

Infertility

Based on findings in animals, female fertility may be compromised by treatment with POMALIDOMIDE [see Nonclinical Toxicology].

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

No dosage adjustment is required for POMALIDOMIDE based on age.
Of the total number of patients in clinical studies of POMALIDOMIDE 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.

Renal Impairment

In patients with severe renal impairment requiring dialysis, the AUC of pomalidomide increased by 38% and the rate of SAE increased by 64% relative to patients with normal renal function; therefore, starting dose adjustment is recommended. For patients with severe renal impairment requiring dialysis, POMALIDOMIDE should be administered after the completion of hemodialysis on dialysis days because exposure of pomalidomide could be significantly decreased during dialysis [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].

Hepatic Impairment

Pomalidomide is metabolized primarily by the liver. Following single dose administration, the AUC of pomalidomide increased 51%, 58%, and 72% in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. Dose adjustment is recommended in patients with hepatic impairment [see DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY].

Smoking Tobacco

Cigarette smoking reduces pomalidomide AUC by 32% due to CYP1A2 induction. Advise patients that smoking may reduce the efficacy of pomalidomide [see CLINICAL PHARMACOLOGY].

SIDE EFFECTS

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

- Fetal Risk [see **WARNINGS AND PRECAUTIONS**]
- Venous and Arterial Thromboembolism [see WARNINGS AND PRECAUTIONS]
- Increased Mortality in Multiple Myeloma when Pembrolizumab Is Added to Dexamethasone and a Thalidomide Analogue [see WARNINGS AND PRECAUTIONS]

Size: 300 x 600 mm
Pharmacode: Front-3218 & Back-3219
Colour : Black
Die Cut

3218

3219

- Hematologic Toxicity [see WARNINGS AND PRECAUTIONS]
- Hepatotoxicity [see **WARNINGS AND PRECAUTIONS**]
- Hypersensitivity Reactions [see WARNINGS AND PRECAUTIONS]
- Dizziness and Confusional State [see WARNINGS AND PRECAUTIONS]
- Neuropathy [see **WARNINGS AND PRECAUTIONS**]
- Risk of Second Primary Malignancies [see WARNINGS AND PRECAUTIONS]
- Tumor Lysis Syndrome [see **WARNINGS AND PRECAUTIONS**]

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 to 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 POMALIDOMIDE + Low-dose Dex (112 patients) or POMALIDOMIDE 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 POMALIDOMIDE + Low-dose Dex (300 patients) or High-dose Dexamethasone (High-dose Dex) (150 patients). The median number of treatment cycles for the POMALIDOMIDE + Low-dose Dex arm was 5. In the POMALIDOMIDE + Low-dose Dex arm, 67% of patients had a dose interruption of POMALIDOMIDE the median time to the first dose interruption of POMALIDOMIDE was 4.1 weeks. Twenty-seven percent of patients had a dose reduction of POMALIDOMIDE the median time to the first dose reduction of POMALIDOMIDE was 4.5 weeks. Eight percent of patients discontinued POMALIDOMIDE 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 POMALIDOMIDE Treatment Arm in Trial 1 *

System Organ Class/Preferred Term	All Adverse Reactions ≥ 10% in Either Arm		Grade 3 or 4 ≥ 5% in Either Arm	
	POMALIDOMIDE* (N = 107)	POMALIDOMIDE + Low-dose Dex (N = 112)	POMALIDOMIDE* (N = 107)	POMALIDOMIDE + Low-dose Dex (N = 112)
System Organ Class/Preferred Term	107 (100)	112 (100)	98 (91.6)	102 (91.1)
Blood and lymphatic system disorders				
Neutropenia †	57 (53.3)	55 (49.1)	51 (47.7)	46 (41.1)
Anemia †	41 (38.3)	47 (42.0)	25 (23.4)	24 (21.4)
Thrombocytopenia †	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 †	< 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 †	62 (57.9)	70 (62.5)	13 (12.1)	19 (17.0)
Pyrexia†	25 (23.4)	36 (32.1)	< 5%	< 5%
Edema peripheral	27 (25.2)	19 (17.0)	0 (0.0)	0 (0.0)
Chills	11 (10.3)	14 (12.5)	0 (0.0)	0 (0.0)
Gastrointestinal disorders				
Nausea †	39 (36.4)	27 (24.1)	< 5%	< 5%
Constipation †	38 (35.5)	41 (36.6)	< 5%	< 5%
Diarrhea	37 (34.6)	40 (35.7)	< 5%	< 5%
Vomiting †	15 (14.0)	16 (14.3)	< 5%	0 (0.0)
Musculoskeletal and connective tissue disorders				
Back pain †	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 †	30 (28.0)	38 (33.9)	21 (19.6)	32 (28.6)
Urinary tract infection †	11 (10.3)	19 (17.0)	2 (1.9)	10 (8.9)
Sepsis †	< 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 †	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 †	< 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 †	38 (35.5)	50 (44.6)	8 (7.5)	14 (12.5)
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)	0 (0.0)
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†	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 †	16 (15.0)	11 (9.8)	9 (8.4)	8 (7.1)

* Regardless of attribution of relatedness to POMALIDOMIDE.

† POMALIDOMIDE 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.

‡ Serious adverse reactions were reported in at least 2 patients in any POMALIDOMIDE treatment arm. Data cutoff: 01 March 2013

Table 3:Adverse Reactions in Trial 2

System Organ Class/Preferred Term	All Adverse Reactions (≥ 5% in POMALIDOMIDE + Low-dose Dex arm, and at least 2% points higher than the High-dose-Dex arm)		Grade 3 or 4 (≥ 1% in POMALIDOMIDE + Low-dose Dex arm, and at least 1% point higher than the High-dose-Dex arm)	
	POMALIDOMIDE + Low-dose Dex (N = 300)	High-dose Dex (N = 150)	POMALIDOMIDE + 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 †	154 (51.3)	31 (20.7)	145 (48.3)	24 (16.0)
Thrombocytopenia	89 (29.7) *	44 (29.3)*	66 (22.0) *	39 (26.0) *
Leukopenia	38 (12.7)	8 (5.3)	27 (9.0)	5 (3.3)
Febrile neutropenia †	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) *	18 (12.0)*
Pyrexia‡	80 (26.7)	35 (23.3)	9 (3.0) *	7 (4.7) *
Edema peripheral	52 (17.3)	17 (11.3)	4 (1.3) *	3 (2.0) *
Pain	11 (3.7) *	3 (2.0) *	5 (1.7)	1 (0.7)
Infections and infestations				
Upper respiratory tract infection †	93 (31.0)	19 (12.7)	9 (3.0)	1 (0.7)
Pneumonia †	58 (19.3)	20 (13.3)	47 (15.7)	15 (10.0)
Neutropenic sepsis †	3 (1.0) *	0 (0.0) *	3 (1.0)	0 (0.0)
Gastrointestinal disorders				
Diarrhea	66 (22.0)	28 (18.7)	3 (1.0) *	2 (1.3)*
Constipation	65 (21.7)	22 (14.7)	7 (2.3)	0 (0.0)
Nausea	45 (15.0)	17 (11.3)	3 (1.0) *	2 (1.3)*
Vomiting	23 (7.7)	6 (4.0)	3 (1.0)	0 (0.0)
Musculoskeletal and connective tissue disorders				
Back pain †	59 (19.7)	24 (16.0)	15 (5.0)	6 (4.0)
Bone pain †	54 (18.0)	21 (14.0)	22 (7.3)	7 (4.7)
Muscle spasms	46 (15.3)	11 (7.3)	1 (0.3) *	1 (0.7)*
Arthralgia	26 (8.7)	7 (4.7)	2 (0.7) *	1 (0.7)*
Pain in extremity	20 (6.7) *	9 (6.0) *	6 (2.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea †	76 (25.3)	25 (16.7)	17 (5.7)	7 (4.7)
Cough	60 (20.0)	15 (10.0)	2 (0.7)*	1 (0.7) *
Chronic obstructive pulmonary disease †	5 (1.7)*	0 (0.0) *	4 (1.3)	0 (0.0)
Nervous system disorders				
Peripheral neuropathy	52 (17.3)	18 (12.0)	5 (1.7) *	2 (1.3) *
Dizziness	37 (12.3)	14 (9.3)	4 (1.3) *	2 (1.3) *
Headache	23 (7.7)	8 (5.3)	1 (0.3) *	0 (0.0) *
Tremor	17 (5.7)	2 (1.3)	2 (0.7) *	0 (0.0) *
Depressed level of consciousness	5 (1.7)*	0 (0.0) *	3 (1.0)	0 (0.0)
Metabolism and nutrition disorders				
Decreased appetite	38 (12.7)	12 (8.0)	3 (1.0) *	2 (1.3) *
Hypokalemia	28 (9.3) *	12 (8.0) *	12 (4.0)	4 (2.7)
Hypocalcemia	12 (4.0) *	9 (6.0) *	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) *	0 (0.0)*
Hyperhidrosis	15 (5.0)	1 (0.7)	0 (0.0) *	0 (0.0)*
Investigations				
Neutrophil count decreased	15 (5.0)	1 (0.7)	14 (4.7)	1 (0.7)
Platelet count decreased	10 (3.3) *	3 (2.0) *	8 (2.7)	2 (1.3)
White blood cell count decreased	8 (2.7) *	1 (0.7) *	8 (2.7)	0 (0.0)
Alanine aminotransferase increased	7 (2.3) *	2 (1.3) *	5 (1.7)	0 (0.0)
Aspartate aminotransferase increased	4 (1.3) *	2 (1.3) *	3 (1.0)	0 (0.0)
Lymphocyte count decreased	3 (1.0) *	1 (0.7) *	3 (1.0)	0 (0.0)
Renal and urinary disorders				
Renal failure	31 (10.3) *	18 (12.0) *	19 (6.3)	8 (5.3)
Injury, poisoning and procedural complications				
Femur fracture †	5 (1.7) *	1 (0.7) *	5 (1.7)	1 (0.7)
Reproductive system and breast disorders				
Pelvic pain	6 (2.0) *	3 (2.0) *	4 (1.3)	0 (0.0)

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

‡ 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 POMALIDOMIDE 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

Postmarketing Experience

The following adverse reactions have been identified during post approval use of POMALIDOMIDE. 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: Pancytopenia, tumor lysis syndrome, allergic reactions (e.g., angioedema, urticaria), elevated liver enzymes, hepatic failure (including fatal cases), hepatitis B virus reactivation, herpes zoster, gastrointestinal hemorrhage, basal cell carcinoma and squamous cell carcinoma of the skin.

PHARMACOLOGICAL PROPERTIES

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.

Pharmacodynamics

Pomalidomide exposure-response analyses showed that there was no relationship between systemic pomalidomide exposure level and efficacy or safety following pomalidomide dose of 4 mg.

Cardiac Electrophysiology

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.

Pharmacokinetics

In patients with multiple myeloma who received POMALIDOMIDE 4 mg daily alone or in combination with dexamethasone, pomalidomide steady-state drug exposure was characterized by AUC of 860 ng.h/mL (CV% = 37%) and Cmax of 75 ng/mL (CV% = 32%).

Absorption

Following administration of single oral doses of POMALIDOMIDE the maximum plasma concentration (Cmax) for pomalidomide occurs at 2 and 3 hours postdose.

Effect of Food

Co-administration of POMALIDOMIDE with a high-fat meal (approximately 50% of the total caloric content) and high-calorie meal (approximately 800 to 1000 calories) (the meal contained approximately 150, 250, and 500 to 600 calories from protein, carbohydrates, and fat, respectively) delays the Tmax by 2.5 hours, decreased mean plasma Cmax and AUC in healthy volunteers by about 27% and 8%, respectively.

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 postdose (~ Tmax) 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-gp.

Elimination

Pomalidomide has a mean total body clearance (CL/F) of 7-10 L/h. 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.

Metabolism

Pomalidomide is primarily metabolized in the liver by CYP1A2 and CYP3A4. Minor contributions from CYP2C19 and CYP2D6 were also observed *in vitro*.

Excretion

Following a single oral administration of [^{14}C]-pomalidomide 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.

Specific Populations

Age (61 to 85 years old), sex and race had no clinically significant effect on the systemic exposure of pomalidomide. The pharmacokinetics of pomalidomide is unknown in pediatric patients.

Renal Impairment

Pomalidomide pharmacokinetic parameters were not significantly affected in patients with moderate (30 mL/min ≤ CrCL < 60 mL/min) or severe (15 mL/min ≤ CrCL < 30 mL/min) renal impairment relative to patients with normal renal function (CrCL ≥ 60 mL/min). Mean exposure (AUC) to pomalidomide increased by 38% in patients with severe renal impairment requiring dialysis (CrCL < 30 mL/min requiring dialysis) and 40% in patients with end stage renal disease (CrCL < 15 mL/min) on non-dialysis days. In patients with severe renal impairment requiring dialysis, the estimated dialysis clearance is approximately 12 L/h which is higher than pomalidomide total body clearance, indicating hemodialysis will remove pomalidomide from the blood circulation.

Hepatic Impairment

Mean exposure (AUC) increased by 51%, 58% and 72% in subjects with mild, moderate or severe hepatic impairment as defined by Child-Pugh criteria, respectively.

Drug Interaction Studies

Co-administration of POMALIDOMIDE with the following drugs did not increase pomalidomide exposure to a clinically significant extent: ketoconazole (a strong CYP3A4 and P-gp inhibitor), carbamazepine (a strong CYP3A4 inducer) and dexamethasone (a weak to moderate inducer of CYP3A4). Co-administration of POMALIDOMIDE with drugs that are CYP1A2 inducers has not been studied.

CYP1A2 Inhibitors

Co-administration of fluvoxamine (a strong CYP1A2 inhibitor) with POMALIDOMIDE increased mean [90% confidence interval] pomalidomide exposure by 125% [98% to 157%] compared to POMALIDOMIDE alone in healthy subjects. Co-administration of fluvoxamine in the presence of ketoconazole (a strong CYP3A4 and P-gp inhibitor) with POMALIDOMIDE increased mean pomalidomide exposure by 146% [126% to 167%] compared to POMALIDOMIDE administered alone in healthy subjects, indicating the predominant effect of CYP1A2 inhibition in the increase of pomalidomide exposure [see DOSAGE AND ADMINISTRATION and DRUG INTERACTIONS].

Strong CYP3A4 and P-gp Inhibitors

Co-administration of ketoconazole (a strong CYP3A4 and P-gp inhibitor) in 16 healthy male subjects increased AUC of pomalidomide by 19% compared to POMALIDOMIDE administered alone.

Drugs That Induce Pomalidomide Metabolism

Strong CYP1A2 Inducers

Co-administration of POMALIDOMIDE 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 AUC of pomalidomide by 20% with a 90% confidence interval [13% to 27%] compared to when pomalidomide was administered alone.

Dexamethasone

Co-administration of multiple doses of 4 mg POMALIDOMIDE 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 to when pomalidomide was administered alone.

Smoking

In 14 healthy male subjects who smoked 25 cigarettes per day for a total of 10 days, after single oral dose of 4 mg POMALIDOMIDE Cmax of pomalidomide increased 14% while AUC of pomalidomide decreased 32%, compared to that in 13 healthy male volunteers who were non-smokers.

In Vitro Studies

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

Availability:

Alu-Alu Blister Pack x 10's (Box of 30's)

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction

Manufactured by:

HETERO

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