Dr.Reddy's

POMARZA

POMARZA 1mg, 2mg, 3mg & 4mg.

1. NAME OF THE MEDICINAL PRODUCT
POMARZA 1 (POMALIDOMIDE CAPSULES 1mg)
POMARZA 2 (POMALIDOMIDE CAPSULES 2mg)
POMARZA 3 (POMALIDOMIDE CAPSULES 3mg)
POMARZA 4 (POMALIDOMIDE CAPSULES 4mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains 1 mg of pomalidomide.
Each hard capsule contains 2 mg of pomalidomide.
Each hard capsule contains 3 mg of pomalidomide.
Each hard capsule contains 4 mg of pomalidomide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard capsules.
POMARZA 1 (POMALIDOMIDE CAPSULES 1mg): Light yellow to yellow colored powder filled into hard gelatin capsule shells with purple colored cap and dark pink colored body imprinted "Y" and '1mg' on cap & '520' on body with white ink
POMARZA 2 (POMALIDOMIDE CAPSULES 2mg): Light yellow to yellow colored powder filled into hard gelatin capsule shells with purple colored cap and pink opaque colored body imprinted "Y" and '2mg' on cap & '519' on body with white ink
POMARZA 3 (POMALIDOMIDE CAPSULES 3mg): Light yellow to yellow colored powder filled into hard gelatin capsule shells with purple colored cap and violet opaque colored body imprinted "Y" and '3mg' on cap & '518' on body with white ink
POMARZA 4 (POMALIDOMIDE CAPSULES 4mg): Light yellow to yellow colored powder filled into hard gelatin capsule shells with purple colored cap and purple opaque colored body imprinted "Y" and '4mg' on cap & '517' on body with white ink

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
POMARZA in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

POMARZA in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration
Treatment must be initiated and monitored under the supervision of physicians experienced in the management of multiple myeloma.
Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Posology
Pomalidomide in combination with bortezomib and dexamethasone
The recommended starting dose of Pomarzais 4 mg orally once daily on Days 1 to 14 of repeated 21-day cycles.
Pomalidomide is administered in combination with bortezomib and dexamethasone, as shown in Table 1. The recommended starting dose of bortezomib is 1.3 mg/m^2 intravenous or subcutaneous once daily, on the days shown in Table 1. The recommended dose of dexamethasone is 20 mg orally once daily, on the days shown in Table 1.
Treatment with pomalidomide combined with bortezomib and dexamethasone should be given until disease progression or until unacceptable toxicity occurs.

Table 1. Recommended dosing schema for Pomarzain combination with bortezomib and dexamethasone

Cycle 1-8	Day (of 21-day cycle)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pomalidomide (4 mg)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•						
Bortezomib (1.3 mg/m^2)	•	•							•				•								
Dexamethasone (20 mg)*	•	•			•	•			•	•			•	•							

Cycle 9 onwards	Day (of 21-day cycle)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pomalidomide (4 mg)	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•						
Bortezomib (1.3 mg/m^2)	•								•												
Dexamethasone (20 mg) *	•	•							•	•											

* For patients > 75 years of age, see Special populations.

Pomalidomide dose modification or interruption
To initiate a new cycle of pomalidomide, the neutrophil count must be ≥ 1 x 10^9/l and the platelet count must be ≥ 50 x 10^9/l.
Instructions on dose interruptions or reductions for pomalidomide related adverse reactions are outlined in the Table 2 and dose levels are defined in Table 3 below:

Table 2. Pomalidomide dose modification instructions[*]

Toxicity	Dose modification
Neutropenia* ANC** < 0.5 x 10^9/l or Febrile neutropenia (fever ≥ 38.5°C and ANC <1 x 10^9/l)	Interrupt pomalidomide treatment for remainder of cycle. Follow CBC*** weekly.
ANC return to ≥ 1 x 10^9/l	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop < 0.5 x 10^9/l	Interrupt pomalidomide treatment.
ANC return to ≥ 1 x 10^9/l	Resume pomalidomide treatment at one dose level lower than the previous dose.
Thrombocytopenia • Platelet count < 25 x 10^9/l	Interrupt pomalidomide treatment for remainder of cycle. Follow CBC*** weekly.
• Platelet count return to ≥ 50 x 10^9/l	Resume pomalidomide treatment at one dose level lower than previous dose.
• For each subsequent drop < 25 x 10^9/l	Interrupt pomalidomide treatment.
• Platelet count return to ≥ 50 x 10^9/l	Resume pomalidomide treatment at one dose level lower than the previous dose.
Rash Rash = Grade 2-3	Consider dose interruption or discontinuation of pomalidomide treatment.
Rash = Grade 4 or blistering (including angioedema, anaphylactic reaction, exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected)	Permanently discontinue treatment (see section 4.4).
Other Other ≥ Grade 3 pomalidomide-related adverse events	Interrupt pomalidomide treatment for remainder of cycle. Resume at one dose level lower than previous dose at next cycle (adverse event must be resolved or improved to ≤ Grade 2 before restarting dosing).

[*] Dose modification instructions in this table are applicable to pomalidomide in combination with bortezomib and dexamethasone and to pomalidomide in combination with dexamethasone.
*In case of neutropenia, the physician should consider the use of growth factors.
**ANC – Absolute Neutrophil Count;
***CBC – Complete Blood Count.

Table 3. Pomalidomide dose reduction[*]

Dose level	Oral pomalidomide dose
Starting dose	4 mg
Dose level -1	3 mg
Dose level -2	2 mg
Dose level -3	1 mg

[*] Dose reduction in this table is applicable to pomalidomide in combination with bortezomib and dexamethasone and to pomalidomide in combination with dexamethasone.

If adverse reactions occur after dose reductions to 1 mg, then the medicinal product should be discontinued.

Strong CYP1A2 inhibitors
If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50% (see sections 4.5 and 5.2).

Bortezomib dose modification or interruption
For instructions on dose interruptions or reductions for bortezomib related adverse reactions, physicians should refer to bortezomib Package Insert.

Dexamethasone dose modification or interruption
Instructions on dose interruptions or reductions for low-dose dexamethasone related adverse reactions are outlined in Tables 4 and 5 below. However, dose interruption or resumption decisions are at the physician's discretion per Package Insert.

Table 4. Dexamethasone dose modification instructions

Toxicity	Dose Modification
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Interrupt dose until symptoms are controlled. Add H2 blocker or equivalent and resume at one dose level lower than previous dose.
Oedema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. Resume at one dose level lower than previous dose.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Resume at one dose level lower than previous dose.
Hyperglycaemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed.
Acute pancreatitis	Discontinue dexamethasone from treatment regimen.
Other ≥ Grade 3 dexamethasone related adverse events	Stop dexamethasone dosing until the adverse event resolves to < Grade 2. Resume at one dose level lower than previous dose.

If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be resumed at one dose level lower than the previous dose.

Table 5. Dexamethasone dose reduction

Dose Level	≤ 75 years old Dose (Cycle 1-8: Days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle Cycle ≥ 9: Days 1, 2, 8, 9 of a 21-day cycle)	≤ 75 years old Dose (Cycle 1-8: Days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle Cycle ≥ 9: Days 1, 2, 8, 9 of a 21-day cycle)
Starting Dose	20 mg	10 mg
Dose Level -1	12 mg	6 mg
Dose Level -2	8 mg	4gn

Dexamethasone should be discontinued if the patient is unable to tolerate 8 mg if ≤ 75 years old or 4 mg if > 75 years old.

In case of permanent discontinuation of any component of the treatment regimen, continuation of the remaining medicinal products is at the physician's discretion.

• *Pomalidomide in combination with dexamethasone*
The recommended starting dose of Pomarzais 4 mg orally once daily on Days 1 to 21 of each 28-day cycle.
The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day cycle.
Treatment with pomalidomide combined with dexamethasone should be given until disease progression or until unacceptable toxicity occurs.

Pomalidomide dose modification or interruption
Instructions for dose interruptions or reductions for pomalidomide related adverse reactions are outlined in Table 2 and 3.

Dexamethasone dose modification or interruption
Instructions for dose modification for dexamethasone related adverse reactions are outlined in Table 4. Instructions for dose reduction for dexamethasone related adverse reactions are outlined in Table 6 below. However, dose interruption / resumption decisions are at physician's discretion per the current Package Insert.

Table 6. Dexamethasone dose reduction

Dose Level	≤ 75 years old Days 1, 8, 15 and 22 of each 28 -day cycle	> 75 years old Days 1, 8, 15 and 22 of each 28 -day cycle
Starting Dose	40 mg	20 mg
Dose Level -1	20 mg	12 mg
Dose Level -2	10mg	8 mg

Dexamethasone should be discontinued if the patient is unable to tolerate 10 mg if ≤ 75 years old or 8 mg if > 75 years old.

Special populations
Elderly
• *Pomalidomide in combination with bortezomib and dexamethasone*
No dose adjustment is required for pomalidomide.
For information on bortezomib given in combination with Pomarza, refer to the respective current Package Insert.
For patients >75 years of age, the starting dose of dexamethasone is:
• For Cycles 1 to 8: 10 mg once daily on Days 1, 2, 4, 5, 8, 9, 11 and 12 of each 21-day cycle
• For Cycles 9 and onwards: 10 mg once daily on Days 1, 2, 8 and 9 of each 21-day cycle.

• *Pomalidomide in combination with dexamethasone*
No dose adjustment is required for pomalidomide.
For patients > 75 years of age, the starting dose of dexamethasone is:
• 20 mg once daily on days 1, 8, 15 and 22 of each 28-day cycle.

Renal impairment
No dose adjustment of pomalidomide is required for patients with renal impairment. On haemodialysis days, patients should take their pomalidomide dose following haemodialysis.

Hepatic impairment
Patients with serum total bilirubin > 1.5 x ULN (upper limit of normal range) were excluded from clinical studies. Hepatic impairment has a modest effect on the pharmacokinetics of pomalidomide (see section 5.2). No adjustment of the starting dose of pomalidomide is required for patients with hepatic impairment as defined by the Child-Pugh criteria. However, patients with hepatic impairment should be carefully monitored for adverse reactions and dose reduction or interruption of pomalidomide should be used as needed.

Paediatric population
Outside its authorised indications, pomalidomide has been studied in children aged 4 to 18 years with recurrent or progressive brain tumours, however the results of studies did not allow to conclude that the benefits of such use outweigh the risks. Currently available data are described in section 4.8, 5.1 and 5.2.
There is no relevant use of Pomarza in children aged 0-17 years for the indication of multiple myeloma.

Method of administration
Oral use.
Pomarzashould be taken orally at the same time each day. The capsules should not be opened, broken or chewed (see section 6.6). This medicinal product should be swallowed whole, preferably with water, with or without food. If the patient forgets to take a dose of Pomarzaon one day, then the patient should take a normal dose of pomalidomide as scheduled on the next day. Patients should not adjust the dose to make up for a missing dose on previous days.
It is recommended to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.
For information on other medicinal products given in combination with Pomarza, refer to the respective current Package Insert.

4.3 Contraindications
• Pregnancy.
• Women of childbearing potential, unless all the conditions of the pregnancy prevention programme are met (see sections 4.4 and 4.6).
• Male patients unable to follow or comply with the required contraceptive measures (see section 4.4).
• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
For information on other medicinal products given in combination with Pomarza, refer to the respective current Package Insert.

4.4 Special warnings and precautions for use
Teratogenicity
Pomalidomide must not be taken during pregnancy, since a teratogenic effect is expected. Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogen that causes severe life- threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis
The conditions of the Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for women of non-childbearing potential
A female patient or a female partner of a male patient is considered of non-childbearing potential if she meets at least one of the following criteria:
Age ≥ 50 years and naturally amenorrheic for ≥ 1 year*
Premature ovarian failure confirmed by a specialist gynaecologist
Previous bilateral salpingo-oophorectomy, or hysterectomy
XY genotype, Turner syndrome, uterine agenesis.
*Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential.

Counselling
For women of childbearing potential, pomalidomide is contraindicated unless all of the following are met:
• She understands the expected teratogenic risk to the unborn child
• She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
• Even if a woman of childbearing potential has amenorrhoea she must follow all the advice on effective contraception
• She should be capable of complying with effective contraceptive measures
• She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
• She understands the need to commence the treatment as soon as pomalidomide is dispensed following a negative pregnancy test
• She understands the need and accepts to undergo pregnancy testing at least every 4 weeks except in case of confirmed tubal sterilization
• She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide.
The prescriber must ensure that for women of childbearing potential:
• The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
• The patient has acknowledged the aforementioned conditions.
For male patients taking pomalidomide, pharmacokinetic data has demonstrated that pomalidomide is present in human semen during treatment. As a precaution, and taking into account special populations with potentially prolonged elimination time such as hepatic impairment, all male patients taking pomalidomide must meet the following conditions:
• He understands the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential
• He understands the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception, throughout treatment duration, during dose interruption and for 7 days after dose interruptions and/or cessation of treatment. This includes vasectomised males who should wear a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential as seminal fluid may still contain pomalidomide in the absence of spermatozoa.
• He understands that if his female partner becomes pregnant whilst he is taking pomalidomide or 7 days after he has stopped taking pomalidomide, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Contraception
Women of childbearing potential must use two effective methods of contraception for at least 4 weeks before therapy, during therapy, and until at least 4 weeks after pomalidomide therapy and even in case of dose interruption unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.
The following can be considered to be examples of suitable methods of contraception:
• Implant
• Levonorgestrel-releasing intrauterine system
• Medroxyprogesterone acetate depot
• Tubal sterilisation
• Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
• Ovulation inhibitory progesterone-only pills (i.e. desogestrel)
Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4–6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during cotreatment with dexamethasone (see section 4.5).
Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.
Insertion of copper-releasing intrauterine devices is not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with severe neutropenia or severe thrombocytopenia.

Pregnancy testing
According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of pomalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment
A medically supervised pregnancy test should be performed during the consultation, when pomalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with pomalidomide.

Follow-up and end of treatment
A medically supervised pregnancy test should be repeated at least every 4 weeks, including at least 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
Pomalidomide is present in human semen during treatment. As a precaution, and taking into account special populations with potentially prolonged elimination time such as renal impairment, all male patients taking pomalidomide, including those who have had a vasectomy, should use condoms throughout treatment duration, during dose interruption and for 7 days after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.
Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for 7 days following discontinuation of pomalidomide.

Additional precautions
Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to their pharmacist at the end of treatment.
Patients should not donate blood, semen or sperm during treatment (including during dose interruptions) and for 7 days following discontinuation of pomalidomide.
Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule (see section 6.6)

Educational materials, prescribing and dispensing restrictions
In order to assist patients in avoiding foetal exposure to pomalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of pomalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform the patient about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of pomalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens (see section 4.2), and prescriptions for all other patients can be for a maximum duration of 12 weeks.

Haematological events
Neutropenia was the most frequently reported Grade 3 or 4 haematological adverse reaction in patients with relapsed/refractory multiple myeloma, followed by anaemia and thrombocytopenia. Patients should be monitored for haematological adverse reactions, especially neutropenia. Patients should be advised to report febrile episodes promptly. Physicians should observe patients for signs of bleeding including epistaxes, especially with use of concomitant medicinal products known to increase the risk of bleeding (see section 4.8). Complete blood counts should be monitored at baseline, weekly for the first 8 weeks and monthly thereafter. A dose modification may be required (see section 4.2). Patients may require use of blood product support and/or growth factors.

Thromboembolic events
Patients receiving pomalidomide either in combination with bortezomib and dexamethasone or in combination with dexamethasone have developed venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) and arterial thrombotic events (myocardial infarction and cerebrovascular accident). Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling.
Anti-coagulation therapy (unless contraindicated) is recommended, (such as acetylsalicylic acid, warfarin, heparin or clopidogrel), especially in patients with additional thrombotic risk factors. A decision to take prophylactic measures should be made after a careful assessment of the individual patient's underlying risk factors. Patients received prophylactic acetylsalicylic acid or alternative anti-thrombotic therapy. The use of erythropoietic agents carries a risk of thrombotic events including thromboembolism. Therefore, erythropoietic agents, as well as other agents that may increase the risk of thromboembolic events, should be used with caution.

Thyroid disorders
Cases of hypothyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

Peripheral neuropathy
Patients with ongoing ≥ Grade 2 peripheral neuropathy were excluded from treatment with pomalidomide. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide.

Significant cardiac dysfunction
Patients with significant cardiac dysfunction (congestive heart failure [NY Heart Association Class III or IV]; myocardial infarction within 12 months of starting study; unstable or poorly controlled angina pectoris) were excluded from treatment with pomalidomide. Cardiac events, including congestive cardiac failure, pulmonary oedema and atrial fibrillation (see section 4.8), have been reported, mainly in patients with pre-existing cardiac disease or cardiac risk factors. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide, including periodic monitoring for signs or symptoms of cardiac events.

Tumour lysis syndrome
Patients at greatest risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Second Primary Malignancies
Second primary malignancies, such as non-melanoma skin cancer, have been reported in patients receiving pomalidomide (see section 4.8). Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

Allergic reaction and severe skin reactions
Angioedema, anaphylactic reaction and severe dermatologic reactions including SJS, TEN and DRESS have been reported with the use of pomalidomide (see Section 4.8). Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Pomalidomide must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Patients with a prior history of serious allergic reactions associated with thalidomide or lenalidomide were excluded from treatment. Such patients may be at higher risk of hypersensitivity reactions and should not receive pomalidomide. Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued permanently for angioedema and anaphylactic reaction.

Dizziness and confusion
Dizziness and confusional state have been reported with pomalidomide. Patients must avoid situations where dizziness or confusion may be a problem and not to take other medicinal products that may cause dizziness or confusion without first seeking medical advice.

Interstitial lung disease (ILD)
ILD and related events, including cases of pneumonitis, have been observed with pomalidomide. Careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. Pomalidomide should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and the risks.

Hepatic disorders
Markedly elevated levels of alanine aminotransferase and bilirubin have been observed in patients treated with pomalidomide (see section 4.8). There have also been cases of hepatitis that resulted in discontinuation of pomalidomide. Regular monitoring of liver function is recommended for the first 6 months of treatment with pomalidomide and as clinically indicated thereafter.

Infections
Reactivation of hepatitis B has been reported rarely in patients receiving pomalidomide in combination with dexamethasone who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure, resulting in discontinuation of pomalidomide. Hepatitis B virus status should be established before initiating treatment with pomalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when pomalidomide in combination with dexamethasone is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Progressive multifocal leukoencephalopathy (PML)
Cases of progressive multifocal leukoencephalopathy, including fatal cases, have been reported with pomalidomide. PML was reported several months to several years after starting the treatment with pomalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.
The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if an alternative diagnosis can be established.
If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, pomalidomide must be permanently discontinued.
For information on other medicinal products given in combination with Pomarza, refer to the respective current Package Insert.

4.5 Interaction with other medicinal products and other forms of interaction
Effect of Pomalidomide on other medicinal products
Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug interactions due to P450 isoenzyme inhibition or induction or transporter inhibition when co-administered with substrates of these enzymes or transporters. The potential for such drug-drug interactions, including the potential impact of pomalidomide on the pharmacokinetics of combined oral contraceptives, has not been evaluated clinically (see section 4.4 Teratogenicity).

Effect of other medicinal products on Pomalidomide
Pomalidomide is partly metabolised by CYP1A2 and CYP3A4/5. It is also a substrate for P-glycoprotein. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased mean exposure to pomalidomide compared to pomalidomide plus ketoconazole. Co- administration of fluvoxamine alone with pomalidomide increased mean exposure to pomalidomide compared to pomalidomide alone. If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

Dexamethasone
Co-administration of multiple doses of up to 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of several CYP enzymes including CYP3A) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.
The effect of dexamethasone on warfarin is unknown. Close monitoring of warfarin concentration is advised during treatment.
For information on other medicinal products given in combination with Pomarza, refer to the respective current Package Insert.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential / Contraception in males and females
Women of childbearing potential should use two effective methods of contraception. If pregnancy occurs in a woman treated with pomalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking pomalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.
Pomalidomide is present in human semen. As a precaution, all male patients taking pomalidomide should use condoms throughout treatment duration, during dose interruption and for 7 days after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception (see sections 4.3 and 4.4).

Pregnancy
A teratogenic effect of pomalidomide in humans is expected. Pomalidomide is contraindicated during pregnancy and in women of childbearing potential, except when all the conditions for pregnancy prevention have been met, see section 4.3 and section 4.4.

Breast-feeding
It is not known if pomalidomide is excreted in human milk. Pomalidomide was detected in milk of lactating rats following administration to the mother. Because of the potential for adverse reactions in nursing infants from pomalidomide, a decision should be made whether to discontinue nursing or to discontinue the medicinal product, taking into account the benefit of breast-feeding for the child and the benefit of the therapy for the mother.

Fertility
Pomalidomide was found to impact negatively on fertility and be teratogenic in animals. Pomalidomide crossed the placenta and was detected in foetal blood following administration to pregnant rabbits.

4.7 Effects on ability to drive and use machines
Pomalidomide has minor or moderate influence on the ability to drive and use machines.
Fatigue, depressed level of consciousness, confusion, and dizziness have been reported with the use of pomalidomide. If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks while being treated with pomalidomide.

4.8 Undesirable effects
Summary of the safety profile
• *Pomalidomide in combination with bortezomib and dexamethasone*
The most commonly reported blood and lymphatic system disorders were neutropenia, thrombocytopenia and anaemia. The most frequently reported adverse reaction was peripheral sensory neuropathy. The most commonly reported Grade 3 or 4 adverse reactions were blood and lymphatic system disorders including neutropenia, thrombocytopenia and anaemia. The most commonly reported serious adverse reaction was pneumonia.
Other serious adverse reactions reported included pyrexia, lower respiratory tract infection, pulmonary embolism, influenza, and acute kidney injury.

• *Pomalidomide in combination with dexamethasone*
The most commonly reported adverse reactions have been blood and lymphatic system disorders including anaemia, neutropenia and thrombocytopenia; in general disorders and administration site conditions including fatigue, pyrexia and oedema peripheral; and in infections and infestations including pneumonia. Peripheral neuropathy adverse reactions were reported and venous embolic or thrombotic (VTE) adverse reactions were reported. The most commonly reported Grade 3 or 4 adverse reactions were in the blood and lymphatic system disorders including neutropenia, anaemia and thrombocytopenia; in infections and infestations including pneumonia; and in general disorders and administration site conditions including fatigue, pyrexia and oedema peripheral. The most commonly reported serious adverse reaction was pneumonia. Other serious adverse reactions reported included febrile neutropenia, neutropenia, thrombocytopenia and VTE adverse reactions.
Adverse reactions tended to occur more frequently within the first 2 cycles of treatment with pomalidomide.

Tabulated list of adverse reactions
• *Pomalidomide in combination with bortezomib and dexamethasone*
The adverse reactions observed in patients treated with pomalidomide in combination with bortezomib and dexamethasone are listed in Table 7 by system organ class (SOC) and frequency for all adverse reactions and for Grade 3 or 4 adverse reactions.
Frequencies for Pom+Btz+Dex (any grade) are defined in accordance with current guidance, as: very common, common and uncommon.

Table 7. All Adverse Reactions (ADRs) reported in patients treated with pomalidomide in combination with bortezomib and dexamethasone.

System Organ Class/ Preferred Term	All Adverse Reactions/ Frequency	Grade 3~4 Adverse Reactions/ Frequency
Infections and infestations	**Very Common** Pneumonia Bronchitis Upper respiratory tract infection Viral upper respiratory tract infection **Common** Sepsis Septic shock Clostridium difficile colitis Respiratory tract infection Lower respiratory tract infection Lung infection Influenza Bronchiolitis Urinary tract infection	**Very Common** Pneumonia **Common** Sepsis Septic shock Clostridium difficile colitis Bronchitis Upper respiratory tract infection Respiratory tract infection Lower respiratory tract infection Lung infection Influenza Bronchiolitis Urinary tract infection
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common Basal cell carcinoma	
Blood and lymphatic system disorders	**Very Common** Neutropenia Thrombocytopenia Leucopenia Anaemia **Common** Febrile neutropenia Lymphopenia	**Very Common** Neutropenia Thrombocytopenia Anaemia **Common** Febrile neutropenia Leucopenia Lymphopenia

POMARZA Leaflet 150099678

320 mm

650 mm

Metabolism and nutrition disorders	**Very Common** Hypokalaemia Hyperglycaemia **Common** Hypomagnesaemia Hypocalcaemia Hypophosphataemia Hyperkalaemia Hypercalcaemia	**Common** Hypokalaemia Hyperglycaemia Hypomagnesaemia Hypocalcaemia Hypophosphataemia Hyperkalaemia Hypercalcaemia
Psychiatric disorders	**Very Common** Insomnia **Common** Depression	**Common** Depression Insomnia
Nervous system disorders	**Very Common** Peripheral sensory neuropathy Dizziness Tremor **Common** Syncope Peripheral sensorimotor neuropathy Paraesthesia Dysgeusia	**Common** Syncope Peripheral sensory neuropathy Peripheral sensorimotor neuropathy **Uncommon** Dizziness Tremor
Eye disorders	**Common** Cataract	**Common** Cataract
Cardiac disorders	**Common** Atrial fibrillation	**Common** Atrial fibrillation
Vascular disorders	**Very Common** Deep vein thrombosis Hypotension Hypertension	**Common** Hypotension Hypertension **Uncommon** Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea Cough **Common** Pulmonary embolism	**Common** Pulmonary embolism Dyspnoea
Gastrointestinal disorders	**Very Common** Diarrhoea Vomiting Nausea Constipation **Common** Abdominal pain Abdominal pain upper Stomatitis Dry mouth Abdominal distension	**Common** Diarrhoea Vomiting Abdominal pain Constipation **Uncommon** Abdominal pain upper Stomatitis Nausea Abdominal distension
Skin and subcutaneous tissue disorders	**Common** Rash	**Common** Rash
Musculoskeletal and connective tissue disorders	**Very Common** Muscular weakness Back pain **Common** Bone pain Muscle spasms	**Common** Muscular weakness Back pain **Uncommon** Bone pain
Renal and urinary disorders	**Common** Acute kidney injury Chronic kidney injury Urinary retention	**Common** Acute kidney injury Chronic kidney injury Urinary retention
General disorders and administration site conditions	**Very Common** Fatigue Pyrexia Oedema peripheral **Common** Non-cardiac chest pain Oedema	**Common** Fatigue Pyrexia Non-cardiac chest pain Oedema peripheral Oedema
Investigations	**Common** Alanine aminotransferase increased Weight decreased	**Common** Weight decreased
Injury, poisoning and procedural complications	**Common** Fall	**Uncommon** Fall

Tabulated list of adverse reactions

- *Pomalidomide in combination with dexamethasone*

The adverse reactions observed in patients treated with pomalidomide plus dexamethasone are listed below in Table 8 by system organ class (SOC) and frequency for all adverse reactions (ADRs) and for Grade 3 or 4 adverse reactions.

The frequencies of adverse reactions are those reported in the pomalidomide plus dexamethasone treatment and from post-marketing data. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined in accordance with current guidance, as: very common, common and uncommon.

Table 8. ADRs reported in patients treated with pomalidomide in combination with dexamethasone.

System Organ Class/ Preferred Term	All ADRs/Frequency	Grade 3–4 ADRs/Frequency
Infections and infestations	**Very Common** Pneumonia (bacterial, viral and fungal infections, including opportunistic infections) **Common** Neutropenic sepsis Bronchopneumonia Bronchitis Respiratory tract infection Upper respiratory tract infection Nasopharyngitis Herpes zoster	**Very Common** Neutropenic sepsis Pneumonia (bacterial, viral and fungal infections, including opportunistic infections) Bronchopneumonia Respiratory tract infection Upper respiratory tract infection **Common** Bronchitis Herpes zoster
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Uncommon** Basal cell carcinoma of the skin, Squamous cell carcinoma of the skin	**Uncommon** Basal cell carcinoma of the skin, Squamous cell carcinoma of the skin
Blood and lymphatic system disorders	**Very Common** Neutropenia Thrombocytopenia Leucopenia Anaemia **Common** Febrile neutropenia	**Very Common** Neutropenia Thrombocytopenia Anaemia **Common** Febrile neutropenia Leucopenia
Metabolism and nutrition disorders	**Very Common** Decreased appetite **Common** Hyperkalaemia Hyponatraemia	**Very Common** Hyperkalaemia Hyponatraemia **Uncommon** Decreased appetite
Psychiatric disorders	**Common** Confusional state	**Common** Confusional state
Nervous system disorders	**Common** Depressed level of consciousness Peripheral sensory neuropathy Dizziness Tremor	**Common** Depressed level of consciousness **Uncommon** Peripheral sensory neuropathy Dizziness Tremor
Ear and labyrinth disorders	**Common** Vertigo	**Common** Vertigo
Vascular disorders	**Common** Deep vein thrombosis	**Uncommon** Deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea Cough **Common** Pulmonary embolism	**Common** Dyspnoea **Uncommon** Pulmonary embolism Cough
Gastrointestinal disorders	**Very Common** Diarrhoea Nausea Constipation **Common** Vomiting Gastrointestinal haemorrhage	**Common** Diarrhoea Vomiting Constipation **Uncommon** Nausea Gastrointestinal haemorrhage
Hepatobiliary disorders	**Uncommon** Hyperbilirubinaemia	**Uncommon** Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	**Common** Rash Pruritus	**Common** Rash
Musculoskeletal and connective tissue disorders	**Very Common** Bone pain Muscle spasms	**Common** Bone pain **Uncommon** Muscle spasms
Renal and urinary disorders	**Common** Renal failure Urinary retention	**Common** Renal failure **Uncommon** Urinary retention
Reproductive system and breast disorders	**Common** Pelvic pain	**Common** Pelvic pain
General disorders and administration site conditions	**Very Common** Fatigue Pyrexia Oedema peripheral	**Common** Fatigue Pyrexia Oedema peripheral
Investigations	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased

Tabulated list of post-marketing adverse reactions

In addition to the above adverse reactions identified, the following Table 9 is derived from data gathered from post-marketing surveillance.

Frequencies are defined in accordance with current guidance, as: very common, common, uncommon and not known.

Table 9. ADRs reported in post-marketing use in patients treated with pomalidomide.

System Organ Class/ Preferred Term	All Adverse Reactions / Frequency	Grade 3–4 Adverse Reactions / Frequency
Infections and infestations	**Not Known** Hepatitis B reactivation	**Not Known** Hepatitis B reactivation
Blood and lymphatic system disorders	**Common** Pancytopenia	**Common** Pancytopenia
Immune system disorders	**Common** Angioedema Urticaria **Not Known** Anaphylactic reaction	**Common** Angioedema Urticaria **Not Known** Anaphylactic reaction
Endocrine disorders	**Uncommon** Hypothyroidism	
Metabolism and nutrition disorders	**Common** Hyperuricaemia **Uncommon** Tumour lysis syndrome	**Common** Hyperuricaemia **Uncommon** Tumour lysis syndrome
Nervous system disorders	**Common** Intracranial haemorrhage **Uncommon** Cerebrovascular accident	**Uncommon** Cerebrovascular accident Intracranial haemorrhage
Cardiac disorders	**Common** Cardiac failure Atrial fibrillation Myocardial infarction	**Common** Cardiac failure Atrial fibrillation **Uncommon** Myocardial infarction
Respiratory, thoracic and mediastinal disorders	**Common** Epistaxis Interstitial lung disease	**Uncommon** Epistaxis Interstitial lung disease
Hepatobiliary disorders	**Uncommon** Hepatitis	
Skin and subcutaneous tissue disorders	**Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms Toxic Epidermal Necrolysis Stevens-Johnson Syndrome	**Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms Toxic Epidermal Necrolysis Stevens-Johnson Syndrome
Investigations	**Common** Blood uric acid increased	**Uncommon** Blood uric acid increased

Description of selected adverse reactions

Teratogenicity

Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis (see sections 4.6). If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected (see section 4.4).

Neutropenia and thrombocytopenia

In patients receiving combination therapy with pomalidomide, neutropenia occurred in patients. Neutropenia did not lead to pomalidomide discontinuation in any patient and was infrequently serious. Febrile neutropenia (FN) was reported in patients and was serious (see section 4.2 and 4.4).

In patients receiving combination therapy with pomalidomide, thrombocytopenia occurred in patients. Thrombocytopenia was Grade 3 or 4 in patients, led to pomalidomide discontinuation and was serious (see sections 4.2 and 4.4).

Neutropenia and thrombocytopenia tended to occur more frequently within the first 2 cycles of treatment with pomalidomide.

Infection

Infection was the most common non haematological toxicity.

In patients receiving combination therapy with pomalidomide in, infection occurred in patients (Grade 3 or 4). Upper respiratory tract infection and pneumonia were the most frequently occurring infections. Fatal infections (Grade 5) occurred in patients. Infections led to pomalidomide discontinuation in patients.

Thromboembolic events

Prophylaxis with acetylsalicylic acid (and other anticoagulants in high risk patients) was mandatory for all patients. Anticoagulation therapy (unless contraindicated) is recommended (see section 4.4).

In patients receiving combination therapy with pomalidomide, venous thromboembolic events (VTE) occurred in patients (Grade 3 or 4). VTE was reported as serious in patients, no fatal reactions were reported, and VTE was associated with pomalidomide discontinuation in patients.

Peripheral neuropathy

Pomalidomide in combination with bortezomib and dexamethasone

Patients with ongoing peripheral neuropathy ≥ Grade 2 with pain within 14 days prior to randomisation were excluded from treatment. Peripheral neuropathy occurred in patients (Grade 3; Grade 4). The patients experiencing peripheral neuropathy had a history of neuropathy at baseline. Peripheral neuropathy led to discontinuation of bortezomib in patients, pomalidomide in patients and dexamethasone in patients, respectively. Refer also to the bortezomib SmPC.

Pomalidomide in combination with dexamethasone

Patients with ongoing peripheral neuropathy ≥ Grade 2 were excluded from treatment. Peripheral neuropathy occurred in patients (Grade 3 or 4). No peripheral neuropathy reactions were reported as serious, and peripheral neuropathy led to dose discontinuation in patients (see section 4.4).

Haemorrhage

Haemorrhagic disorders have been reported with pomalidomide, especially in patients with risk factors such as concomitant medicinal products that increase susceptibility to bleeding. Haemorrhagic events have included epistaxis, intracranial haemorrhage and gastrointestinal haemorrhage.

Allergic reactions and severe skin reactions

Angioedema, anaphylactic reaction and severe cutaneous reactions including SJS, TEN and DRESS have been reported with the use of pomalidomide. Patients with a history of severe rash associated with lenalidomide or thalidomide should not receive pomalidomide (see section 4.4).

Paediatric population

Adverse reactions reported in paediatric patients (aged 4 to 18 years) with recurrent or progressive brain tumours were consistent with the known pomalidomide safety profile in adult patients (see section 5.1).

4.9 Overdose

Pomarza doses as high as 50 mg as a single dose in healthy patients, and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse reactions related to overdose. In available data, pomalidomide was found to be removed by haemodialysis.

In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunomodulating agent, ATC code: L04AX06

Mechanism of action

Pomalidomide has direct anti-myeloma tumoricidal activity, immunomodulatory activities and inhibits stromal cell support for multiple myeloma tumour cell growth. Specifically, pomalidomide inhibits proliferation and induces apoptosis of haematopoietic tumour cells. Additionally, pomalidomide inhibits the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergises with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumour cell apoptosis. Pomalidomide enhances T cell- and natural killer (NK) cell- mediated immunity and inhibits production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide also inhibits angiogenesis by blocking the migration and adhesion of endothelial cells.

Pomalidomide binds directly to the protein cereblon (CRBN), which is part of an E3 ligase complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins-1 (Roc1), and can inhibit the auto-ubiquitination of CRBN within the complex. E3 ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate proteins, and may partially explain the pleiotropic cellular effects observed with pomalidomide treatment.

In the presence of pomalidomide, substrate proteins Aiolos and Ikaros are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. Pomalidomide therapy led to reduction in the levels of Ikaros in patients with relapsed lenalidomide-refractory multiple myeloma.

5.2 Pharmacokinetic properties

Absorption

Pomalidomide is absorbed with a maximum plasma concentration (Cmax) occurring between 2 and 3 hours and is at least 73% absorbed following administration of single oral dose. The systemic exposure (AUC) of pomalidomide increases in an approximately linear and dose proportional manner. Following multiple doses, pomalidomide has an accumulation ratio of 27 to 31% on AUC.

Coadministration with a high-fat and high-calorie meal slows the rate of absorption, decreasing mean plasma Cmax by approximately 27%, but has minimal effect on the overall extent of absorption with an 8% decrease in mean AUC. Therefore, pomalidomide can be administered without regard to food intake.

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 patients at a concentration of approximately 67% of plasma level at 4 hours post-dose (approximately Tmax) after 4 days of once daily dosing at 2 mg. Binding of pomalidomide enantiomers to proteins in human plasma ranges from 12% to 44% and is not concentration dependent.

Biotransformation

Pomalidomide is the major circulating component (approximately 70% of plasma radioactivity) in vivo in healthy subjects who received a single oral dose of [14C]-pomalidomide (2 mg). No metabolites were present at >10% relative to parent or total radioactivity in plasma.

The predominant metabolic pathways of excreted radioactivity are hydroxylation with subsequent glucuronidation, or hydrolysis. 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. Pomalidomide is also a substrate of P-glycoprotein in vitro. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co- administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased mean exposure to pomalidomide compared to pomalidomide plus ketoconazole. Co-administration of fluvoxamine alone with pomalidomide increased mean exposure to pomalidomidecompared to pomalidomide alone. If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide to 50%. Administration of pomalidomide in smokers, with smoking tobacco known to induce the CYP1A2 isoform, had no clinically relevant effect on exposure to pomalidomide compared to that exposure to pomalidomide observed in non-smokers.

Based on data, pomalidomide is not an inhibitor or inducer of cytochrome P-450 isoenzymes, and does not inhibit any drug transporters that were evaluated. Clinically relevant drug-drug interactions are not anticipated when pomalidomide is coadministered with substrates of these pathways.

Elimination

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

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

Pomalidomide is extensively metabolised prior to excretion, with the resulting metabolites eliminated primarily in the urine. The 3 predominant metabolites in urine (formed via hydrolysis or hydroxylation with subsequent glucuronidation) account for approximately 23%, 17%, and 12%, respectively, of the dose in the urine.

CYP dependent metabolites account for approximately 43% of the total excreted radioactivity, while non- CYP dependent hydrolytic metabolites account for 25%, and excretion of unchanged pomalidomide accounted for 10% (2% in urine and 8% in faeces).

Population Pharmacokinetics (PK)

Based on population PK analysis, healthy patients and MM patients had comparable apparent clearance (CL/F) and apparent central volume of distribution (V2/F). In peripheral tissues, pomalidomide was preferentially taken up by tumors with apparent peripheral distribution clearance (Q/F) and apparent peripheral volume of distribution (V3/F) 3.7-fold and 8-fold higher, respectively, than that of healthy patients.

Paediatric population

Following a single oral dose of pomalidomide in children and young adults with recurrent or progressive primary brain tumour, the median Tmax was 2 to 4 hours post-dose. AUC0-24 and AUC0-inf followed similar trends, with total exposure in the range of approximately 700 to 800 h ng/mL at the lower 2 doses, and approximately 1200 h·ng/mL at the high dose. Estimates of half-life were in the range of approximately 5 to 7 hours. There were no clear trends attributable to stratification by age and steroid use at the MTD.

Overall, data suggest that AUC increased nearly proportional to the increase in pomalidomide dose, while the increase in Cmax was generally less than proportional.

The pharmacokinetics of pomalidomide following oral administration dose levels of 1 9.mg/m²/day to 3.4 mg/m²/day were determined in patients with ages from 4 to 20 years with recurrent or progressive paediatric brain tumours. Pomalidomide concentration-time profiles were adequately described with a one compartment PK model with first- order absorption and elimination. Pomalidomide exhibited linear and time-invariant PK with moderate variability. The typical values of CL/F, Vc/F, Ka, lag time of pomalidomide were 3.94 L/h, 43.0 L, 1.45 h-1and 0.454 h respectively. The terminal elimination half-life of pomalidomide was 7.33 hours. Except for body surface area (BSA), none of the tested covariates including age and sex had effect on pomalidomide PK. Although BSA was identified as a statistically significant covariate of pomalidomide CL/F and Vc/F, the impact of BSA on exposure parameters was not deemed clinically relevant.

In general, there is no significant difference of pomalidomide PK between children and adult patients.

Elderly

Based on population pharmacokinetic analyses in healthy patients and multiple myeloma patients, no significant influence of age (19-83 years) on oral clearance of pomalidomide was observed. In clinical studies, no dosage adjustment was required in elderly (> 65 years) patients exposed to pomalidomide. Please see section 4.2.

Renal impairment

Population pharmacokinetic analyses showed that the pomalidomide pharmacokinetic parameters were not remarkably affected in renally impaired patients (defined by creatinine clearance or estimated glomerular filtration rate [eGFR]) compared to patients with normal renal function (CrCl ≥ 60 mL/minute). Mean normalized AUC exposure to pomalidomide was 98.2% in moderate renal impairment patients (eGFR ≥30 to ≤45 mL/minute/1.73 m²) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m²) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide increased by 35.8% in severe renal impairment patients requiring dialysis (CrCl <30 mL/minute requiring dialysis) compared to patients with normal renal function. The mean changes in exposure to pomalidomide in each of these renal impairment groups are not of a magnitude that require dosage adjustments.

Hepatic impairment

The pharmacokinetic parameters were modestly changed in hepatically impaired patients (defined by Child-Pugh criteria) compared to healthy patients. Mean exposure to pomalidomide increased by 51% in mildly hepatically impaired patients compared to healthy patients. Mean exposure to pomalidomide increased by 58% in moderately hepatically impaired patients compared to healthy patients. Mean exposure to pomalidomide increased by 72% in severely hepatically impaired patients compared to healthy patients. The mean increases in exposure to pomalidomide in each of these impairment groups are not of a magnitude for which adjustments in schedule or dose are required (see section 4.2).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Pregelatinized Starch (Starch 1500 Partially Pregelatinized Maize Starch) NF, Anhydrous Lactose (Super Tab 21 AN) NF, Sodium Stearyl Fumarate NF

Capsule Shell 1mg:

Gelatin, Water, Titanium dioxide, FD&C Blue 1, FD&C Red 3 and D&C Red 33

Capsule Shell 2mg:

Gelatin, Water, Titanium dioxide, FD&C Blue 1, FD&C Red 3, D&C Yellow 10 and D&C Red 33

Capsule Shell 3mg:

Gelatin, Water, Titanium dioxide, FD&C Blue 1, FD&C Red 3, FD&C Red 40 and D&C Red 33

Capsule Shell 4mg:

Gelatin, Water, Titanium dioxide, FD&C Blue 1, FD&C Red 3, D&C Red 28 and D&C Red 33

Printing White ink:

Shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, ammonia, purified water, potassium hydroxide & titanium dioxide

Source of Gelatin:

Bovine

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30 Celcius

6.5 Nature and contents of container

Blisters of cold formed triluminate OPA/Alu/PVC with paper backed aluminium foil containing 7 capsules. Such 3 blisters are packed into an outer carton with a pack insert.

6.6 Special precautions for disposal and other handling

Capsules should not be opened or crushed. If powder from pomalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If pomalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.

Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Gloves should then be removed carefully to prevent skin exposure, placed in a sealable plastic polyethylene bag and disposed of in accordance with local requirements. Hands should then be washed thoroughly with soap and water. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Unused medicinal product should be returned to the pharmacist at the end of treatment.

7. NAME OF MANUFACTURER

Dr. Reddy's Laboratories Limited,
Formulation Unit-VII,
Plot No. P1 to P9, Phase-III,
VSEZ, Duvvada,
Visakhapatnam District 530046,
Andhra Pradesh, India

8. NAME OF PRODUCT REGISTRATION HOLDER

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59200 KUALA LUMPUR
MALAYSIA

9. DATE OF REVISION OF THE TEXT

March 2025