SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

POMARZA 1

POMARZA 2

POMARZA 3

POMARZA 4

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

POMARZA 1: each hard gelatin capsule contains 1,0 mg of pomalidomide.

POMARZA 2: each hard gelatin capsule contains 2,0 mg of pomalidomide.

POMARZA 3: each hard gelatin capsule contains 3,0 mg of pomalidomide.

POMARZA 4: each hard gelatin capsule contains 4,0 mg of pomalidomide.

Contains sugar (lactose):

POMARZA 1: each hard gelatin capsule contains 25 mg anhydrous lactose.

POMARZA 2: each hard gelatin capsule contains 50 mg of anhydrous lactose.

POMARZA 3: each hard gelatin capsule contains 75 mg of anhydrous lactose.

POMARZA 4: each hard gelatin capsule contains 100 mg of anhydrous lactose.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsule.

POMARZA 1: Light yellow to yellow coloured powder filled into hard gelatin capsule shells with purple coloured cap and dark pink coloured body imprinted  and 1 mg on cap & '520' on body with white ink.

POMARZA 2: Light yellow to yellow coloured powder filled into hard gelatin capsule shells with purple coloured cap and pink opaque coloured body imprinted  and 2 mg on cap & '519' on body with white ink.

POMARZA 3: Light yellow to yellow coloured powder filled into hard gelatin capsule shells with purple coloured cap and violet opaque coloured body imprinted  and 3 mg on cap & '518' on body with white ink.

POMARZA 4: Light yellow to yellow coloured powder filled into hard gelatin capsule shells with purple coloured cap and purple opaque coloured body imprinted  and 4 mg on cap & '517' on body with white ink.

WARNING: SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS

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 section 4.6).

If Pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected.

BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE CHANCE OF FOETAL EXPOSURE TO POMARZA AS NEGLIGIBLE AS POSSIBLE, POMARZA IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME.

UNDER THIS RESTRICTED DISTRIBUTION PROGRAMME, ONLY PRECRIBERS REGISTERED WITH THE PROGRAMME ARE ALLOWED TO PRESCRIBE THE PRODUCT AND PHARMACISTS REGISTERED WITH THE PROGRAMME ARE ALLOWED TO DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUIREMENTS OF THE RISK MANAGEMENT PROGRAMME.

WARNING: VENOUS THROMBO EMBOLISM

Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMARZA. Consider prophylactic measures after assessing an individual patient's underlying risk factors (see section 4.4).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- POMARZA in combination with bortezomib and dexamethasone (PBd) is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.
- POMARZA in combination with dexamethasone (Pd) 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 a proteasome inhibitor (e.g., bortezomib), and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

Posology

Treatment must be initiated and monitored under the supervision of a medical practitioner experienced in the management of multiple myeloma.

<u>In combination with Bortezomib and Dexamethasone (PBd) – patients with relapsed or refractory multiple myeloma after at least one prior therapy including lenalidomide:</u>

Recommended dosage:

The recommended starting dose of POMARZA is 4 mg orally once daily on days 1-14 for each 21-day cycle.

The recommended dose of bortezomib is:

- For cycles 1-8: 1.3mg/m^2 on Days 1, 4, 8 and 11 of a 21-day cycle.

- From cycle 9 onwards: 1.3mg/m^2 on Days 1 and 8 of a 21-day cycle.

The recommended dose of dexamethasone is:

- For cycles 1-8: 20 mg orally once daily on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle.
- From cycle 9 onwards: 20 mg orally once daily on days 1, 2, 8, and 9 of a 21-day cycle.

For patients greater than 75 years of age, see section Special populations below.

Dosing is to be continued or modified based upon clinical and laboratory findings.

It is recommended that treatment be discontinued upon progression of disease.

In combination with Dexamethasone (Pd) – patients with relapsed and refractory multiple myeloma after at least two prior therapies including lenalidomide and a proteasome inhibitor:

Recommended dosage:

The recommended starting dose of is 4 mg/day taken orally on Days 1-21 of repeated 28-day cycles (21/28 days) until disease progression. The recommended dose of dexamethasone is 40 mg/day on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

Dosing is continued or modified based upon clinical and laboratory findings.

Dose modification or interruption:

Instructions for dose interruptions and reductions for POMARZA related to haematologic adverse reactions are outlined in the table below:

Dose modification instructions for POMARZA for haematologic toxicities:

Toxicity	**Dose modification**
Neutropenia	
• ANC < 500/µL or febrile neutropenia (fever ≥ 38,5 °C and ANC < 1000/µL)	• Interrupt POMARZA treatment, follow CBC weekly. Add G-CSF (at the discretion of the treating doctor)
• Pd regimen: ANC return to ≥ 500/µL	• Resume POMARZA at 3 mg daily
• PBd regimen: ANC return to ≥ 1000/µL	
• For each subsequent drop < 500/µL	• Interrupt POMARZA treatment
• Pd regimen: Return to ≥ 500/µL	• Resume POMARZA at 1 mg less than the previous dose
• PBd regimen: Return to ≥ 1000/µL	

Thrombocytopenia	
• Platelets < 25 000/µL	• Interrupt POMARZA treatment, follow CBC weekly
• Platelets return to > 50 000/µL	• Resume POMARZA treatment at 3 mg daily
• For each subsequent drop < 25 000/µL	• Interrupt POMARZA treatment
• Return to ≥ 50 000/µL	• Resume POMARZA at 1 mg less than previous dose.
ANC = Absolute neutrophil count CBC = complete blood count	

PBd regimen: To initiate a new cycle of POMARZA, the neutrophil count must be ≥ 1000/µL, and the platelet count must be ≥ 50 000/µL.

Pd regimen: To initiate a new cycle of POMARZA, the neutrophil count must be ≥ 500/µL, the platelet count must be ≥ 50 000/µL.

For other Grade 3/4 toxicities judged to be related to POMARZA, stop treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to ≤ Grade 2 at the medical practitioner's discretion.

If toxicities occur after dose reductions to 1 mg, then the medicine should be discontinued.

Dose Adjustment for Co-Administration of CYP1A2 Inhibitors:

If strong inhibitors of CYP1A2 (e.g., fluvoxamine, ciprofloxacin) are co-administered with POMARZA, reduce the recommended starting POMARZA dose to 2 mg (a 50 % reduction for patients with multiple myeloma) (see section below).

PBd regimen: For dose adjustments due to toxicity with bortezomib, refer to the product professional information.

Dexamethasone dose modification instructions:

Toxicity	**Dose modification**
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H_2) blockers or equivalent. Decrease by one dose level if symptoms persist.

Dyspepsia ≥ Grade 3	Interrupt dose until symptoms are controlled. Add H_2 blocker or equivalent and decrease one dose level when dose restarted.
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. When dose restarted decrease dose by one dose level.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Restart with dose decreased by one level.
Hyperglycaemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic medicines as needed
Acute pancreatitis	Discontinue patient from dexamethasone treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤ Grade 2. Resume with dose reduced by one level.

Discontinuation of POMARZA

POMARZA interruption or discontinuation should be considered for Grade 2-3 skin rash.

POMARZA must be discontinued for angioedema, anaphylaxis, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or medicine reaction with eosinophilia and systemic symptoms (DRESS) is suspected, and should not be resumed following discontinuation for these reactions.

Dose reduction levels (≤ 75 years of age): Starting dose 40 mg; dose level -1 20 mg; dose level-2 10 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

Dose reduction levels (> 75 years of age): Starting dose 20 mg; dose level -1 12 mg; dose level -2 8 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

Special populations

Elderly population

No dose adjustment is required for POMARZA.

Pd regimen after at least 2 prior therapies:

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 treatment cycle.

PBd regimen after at least one prior therapy:

For patients > than 75 years of age, the dose of dexamethasone is:

Cycles 1-8: 10 mg once daily on days 1, 2, 4, 5, 8, 9, 11, and 12 of a 21-day cycle. From cycle 9 onwards: 10 mg once daily on days 1, 2, 8, and 9 of a 21-day cycle.

Renal impairment

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

Hepatic impairment

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 and interruption of POMARZA should be carried out as needed.

Paediatric population

The safety and effectiveness of pomalidomide have not been established in paediatric patients with recurrent or progressive brain tumours.

Method of administration

POMARZA should be taken orally at the same time each day. The capsules should not be opened, broken or chewed and should be swallowed whole, preferably with water, with or without food.

4.3 Contraindications

- hypersensitivity to pomalidomide or to any of the excipients listed in section 6.1.
- pregnancy and lactation (see section 4.6).
- females of childbearing potential, unless all the conditions of the pregnancy prevention programme are met (see section 4.4).
- male patients unable to follow or comply with the required contraceptive measures (see section 4.4).

4.4 Special warnings and precautions for use

General

Pregnancy warning

Pomalidomide is a thalidomide analogue. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If POMARZA is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected.

The conditions of the RISK MANAGEMENT PROGRAMME must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for females of non-childbearing potential

A female patient or a female partner of a male patient is considered to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 2 + years*.
- 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 females of childbearing potential, POMARZA 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, 4 weeks before starting treatment, throughout the entire duration of treatment including dose interruptions, and for 4 weeks after the end of treatment.
- Even if a female 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 POMARZA is dispensed

following a negative pregnancy test.

- She understands the need and accepts to undergo pregnancy testing 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 POMARZA.

The prescriber must ensure that for females of childbearing potential:

- The patient complies with the conditions of the RISK MANAGEMENT PROGRAMME, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.

For male patients taking POMARZA, pharmacokinetic data has demonstrated that pomalidomide is present in human semen. As a precaution, all male patients taking POMARZA must meet the following conditions:

- He understands the expected teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential.
- He understands the need for the use of a condom if engaged in sexual activity with a pregnant female or a female of childbearing potential not using effective contraception, during treatment and for 4 weeks after dose interruptions and/or cessation of treatment. Vasectomised males should wear a condom if engaged in sexual activity with a pregnant female 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 POMARZA or for 4 weeks after he has stopped taking POMARZA, he should inform his treating medical practitioner immediately and that it is recommended to refer the female partner to a medical practitioner specialised or experienced in teratology for evaluation and advice.

Contraception

Females of childbearing potential must use two reliable methods of contraception for 4 weeks before therapy, during therapy including dose interruptions, and until 4-weeks after POMARZA therapy 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:

Highly effective methods

- Intra Uterine Device (IUD)
- Hormonal (hormonal implants, levonorgestrel-releasing intrauterine system (IUS)), medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills (e.g., desogestrel)
- Tubal ligation
- Partner's vasectomy

Effective methods

- Male condom
- Diaphragm
- Cervical cap

Because there is an increased risk of venous thromboembolism (VTE) in patients taking combined oral contraceptive pills, medical practitioners should discuss the risk/benefit of contraceptive methods with their patients.

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 co-treatment 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

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/ml must be performed for females of childbearing potential as outlined below. This requirement includes females 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 POMARZA to females of childbearing potential should occur within 7 days of the last pregnancy test.

Prior to starting treatment

A medically supervised pregnancy test should be performed within 7 days prior to the patient starting POMARZA 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 POMARZA.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated every 4 weeks, including 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 within the 7 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 POMARZA, including those who have had a vasectomy, should use condoms throughout treatment duration, during dose interruption and for 4 weeks 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 4 weeks following discontinuation of POMARZA.

Additional precautions

Patients should be instructed never to give POMARZA to another person and to return any unused capsules to their pharmacist at the end of treatment.

Patients should not donate blood during therapy including dose interruptions and for 4 weeks following discontinuation of POMARZA.

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

Full patient information about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the RISK MANAGEMENT PROGRAMME should be given by the medical practitioner to

females of childbearing potential and, as appropriate, to male patients.

Haematological events

Neutropenia was the most frequently reported Grade 3/4 haematologic adverse reaction (AR) during treatment for relapsed/refractory multiple myeloma, followed by anaemia and thrombocytopenia. Monitor patients for haematologic toxicities, especially neutropenia. Patients should be advised to report febrile episodes promptly. Medical practitioners should observe patients for signs of bleeding including epistaxes, especially with use of concomitant medicines known to increase the risk of bleeding (see section 4.8). Monitor complete blood counts at baseline, weekly for the first 8 weeks and monthly thereafter. A dose modification may be required. Patients may require use of blood product support and/or growth factors.

Thromboembolic events

Patients receiving POMARZA have commonly developed venous thromboembolic events (VTE) (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 medical practitioners 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.

In clinical studies, patients received prophylactic acetylsalicylic acid or alternative antithrombotic therapy.

The use of erythropoietic agents carries a risk of thrombotic events including thromboembolism. Therefore, erythropoietic medicines may increase the risk of thromboembolic events and 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

Appropriate caution should be exercised when considering the treatment of patients with ongoing ≥ Grade 2 peripheral neuropathy with POMARZA.

Significant cardiac dysfunction

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 POMARZA, including periodic monitoring for signs or symptoms of cardiac events.

Tumour lysis syndrome

The 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 POMARZA (see section 4.8). Medical practitioners should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.

Allergic reactions and Serious Skin Reactions

- Angioedema, anaphylaxis and severe dermatologic reactions including Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events can be fatal.
- Patients with a prior history of serious allergic reactions associated with thalidomide or lenalidomide may be at a higher risk of hypersensitivity and should not receive POMARZA. POMARZA interruption or discontinuation should be considered for Grade 2-3 skin rash. POMARZA must be discontinued for angioedema, anaphylaxis, Grade 4 rash, exfoliative or bullous rash or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions.

Dizziness and confusion

Confusion, fatigue, depressed level of consciousness and dizziness have been reported with the use of POMARZA. Patients must avoid situations where dizziness or confusion may be a problem and not to take other medicines 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. POMARZA should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be 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 POMARZA. Regular monitoring of liver function is recommended for the first 6 months of treatment with pomalidomide and as clinically indicated thereafter.

Infection

Reactivation of hepatitis B has been reported in patients receiving POMARZA 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 POMARZA. 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 no 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.

POMARZA contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Effect of POMARZA on other medicines

POMARZA does not cause clinically relevant enzyme inhibition or induction or transporter inhibition when co-administered with substrates of these enzymes or transporters. The potential for such interactions, including the potential impact of POMARZA on exposure of oral contraceptives, has not been evaluated clinically.

Effect of other medicines on POMARZA

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 exposure to pomalidomide by 104 % with a 90 % confidence interval [88 % to 122 %] compared to pomalidomide plus ketoconazole. During evaluation of the contribution of a CYP1A2 inhibitor alone to metabolism changes, co-administration of fluvoxamine alone with pomalidomide increased mean exposure to pomalidomide by 125 % with a 90 % confidence interval [98 % to 156 %] compared to

pomalidomide alone.

If strong inhibitors of CYP1A2 are co-administered with pomalidomide, reduce the pomalidomide dose by 50 % for patients with multiple myeloma (based on the recommended starting doses) (see section 4.2).

Dexamethasone

Co-administration of multiple doses of 4 mg POMARZA 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. Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during treatment.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Females of childbearing potential should use two effective methods of contraception.

If pregnancy occurs in a female treated with POMARZA, treatment must be stopped and the patient should be referred to a medical practitioner specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking POMARZA, it is recommended to refer the female partner to a medical practitioner specialised or experienced in teratology for evaluation and advice.

Pomalidomide is present in human semen. As a precaution, all male patients taking POMARZA should use condoms throughout treatment duration, during dose interruption and for 4 weeks after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception (see section 4.4).

Pregnancy

POMARZA is contraindicated during pregnancy and in women of childbearing potential (see section 4.3).

Breastfeeding

Breastfeeding of infants is contraindicated in mothers taking POMARZA (see section 4.3).

4.7 Effects on ability to drive and use machines

POMARZA may cause confusion, fatigue, depressed level of consciousness and dizziness and affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision. 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

PBd Treatment Regimen – for relapsed and refractory multiple myeloma after at least one prior therapy including lenalidomide:

Table 1: Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse effect
Infections and infestations	Frequent	Upper respiratory tract infection, pneumonia, bronchitis, viral upper respiratory infection, influenza, urinary tract infection, respiratory tract infection, lower respiratory tract infection, sepsis, septic shock, Clostridium difficile colitis, lung infection, bronchiolitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequent	Basal cell carcinoma
Blood and lymphatic system disorders	Frequent	Neutropenia, thrombocytopenia[4], anaemia[4], leukopenia, lymphopenia, febrile neutropenia
Metabolism and nutrition disorders	Frequent	Hypokalemia, hyperglycemia, hypomagnesemia, hypocalcemia, hypophosphatemia, hyperkalemia, hypercalcemia
Psychiatric disorders	Frequent	Insomnia, depression
Nervous system disorders	Frequent	Peripheral sensory neuropathy, dizziness, tremor, dysgeusia, syncope, peripheral sensorimotor neuropathy, paresthesia
Eye disorders	Frequent	Cataract
Cardiac disorders	Frequent	Atrial fibrillation
Vascular disorders	Frequent	Hypotension, hypertension, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	Frequent	Cough, dyspnoea, pulmonary embolism
Gastro-intestinal disorders	Frequent	Constipation, diarrhoea, nausea[4], vomiting[4], abdominal pain, abdominal pain upper, stomatitis, dry mouth, abdominal distension
Skin and sub-cutaneous tissue disorders	Frequent	Rash
Musculo-skeletal and connective tissue disorders	Frequent	Back pain, muscular weakness, muscle spasms, bone pain

Renal and urinary disorders	Frequent	Acute kidney injury, chronic kidney disease, urinary retention
General disorders and administration site conditions	Frequent	Fatigue, oedema peripheral, pyrexia, non-cardiac chest pain, oedema
Investigations	Frequent	Weight decreased, alanine aminotransferase increased[4]
Injury, poisoning and procedural complications	Frequent	Fall

Pd Treatment Regimen – in relapsed and refractory multiple myeloma after at least two prior therapies including lenalidomide and a proteasome inhibitor:

Table 2: Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse effect
Infections and infestations	Frequent	Pneumonia (bacterial, viral and fungal infections, including opportunistic infections), neutropenic sepsis, bronchopneumonia, bronchitis, respiratory tract infection, upper respiratory tract infection, nasopharyngitis, herpes zoster
	Frequency unknown	Hepatitis B reactivation
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Less frequent	Basal cell carcinoma, squamous cell carcinoma of the skin
Blood and lymphatic system disorders	Frequent	Neutropenia, thrombocytopenia, anaemia, leucopenia, febrile neutropenia, pancytopenia
Metabolism and nutrition disorders	Frequent	Decreased apetite, hyperkalemia, hyponatraemia, hyperuricaemia
	Less frequent	Tumour lysis syndrome
Psychiatric disorders	Frequent	Confusional state
Nervous system disorders	Frequent	Depressed level of consciousness, peripheral sensory neuropathy, dizziness, tremor, intracranial haemorrhage
	Less frequent	Cerebrovascular accident
Ear and labyrinth disorders	Frequent	Vertigo
Cardiac disorders	Frequent	Cardiac failure, atrial fibrillation, myocardial infarction
Vascular disorders	Frequent	Deep vein thrombosis
Immune system disorders	Frequent	Angioedema, urticaria

Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, cough, pulmonary embolism, epistaxis, interstitial lung disease
Gastro-intestinal disorders	Frequent	Diarrhoea, nausea, constipation, vomiting, gastrointestinal haemorrhage
Hepatobiliary disorders	Less frequent	Hyperbilirubinaemia, hepatitis
Skin and sub-cutaneous tissue disorders	Frequent	Rash, pruritus
Musculo-skeletal and connective tissue disorders	Frequent	Bone pain, muscle spasms
Renal and urinary disorders	Frequent	Renal failure, urinary retention
Reproductive system and breast disorders	Frequent	Pelvic pain
General disorders and administration site conditions	Frequent	Fatigue, pyrexia, oedema peripheral
Investigations	Frequent	Decreased neutrophil count, decreased white blood cell count, decreased platelet count, increased alanine aminotransferase, increased blood uric acid increased

Post-marketing data:

Blood and Lymphatic System Disorders: Pancytopenia

Endocrine Disorders: Hypothyroidism

Gastrointestinal Disorders: Gastrointestinal haemorrhage

Hepatobiliary Disorders: Hepatitis, increased liver function tests

Immune System Disorders: Allergic reactions (e.g., angioedema, anaphylaxis, urticaria)

Infections and Infestations: Viral reactivation (such as hepatitis B virus and herpes zoster), progressive multifocal leukoencephalopathy (PML)

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Tumour lysis syndrome, basal cell carcinoma, and squamous cell carcinoma of the skin

Respiratory, Thoracic and Mediastinal Disorders: Interstitial lung disease (ILD), pneumonitis

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson Syndrome, toxic epidermal necrolysis, medicine reaction with eosinophilia and systemic symptoms (DRESS)

Description of selected adverse reactions:

Teratogenicity:

POMARZA is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If POMARZA is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected (see section 4.4 and section 4.6).

Neutropenia and thrombocytopenia:

Neutropenia occurred in patients who received pomalidomide plus low dose dexamethasone (Pom + LD-Dex), and in patients who received high dose dexamethasone (HD-Dex). Neutropenia was Grade 3 or 4 in patients who received Pom + LD-Dex, compared with patients who received HD-Dex. In Pom + LD-Dex treated patients neutropenia was infrequently serious, and did not lead to treatment discontinuation, and was associated with treatment interruption and with dose reduction.

Febrile neutropenia (FN) was experienced in patients who received Pom + LD-Dex, and in no patients who received HD-Dex. All were reported to be Grade 3 or 4. FN was reported to be serious. FN was associated with dose interruption, dose reduction and with no treatment discontinuations.

Thrombocytopenia occurred in patients who received Pom + LD-Dex, and patients who received HD-Dex. Thrombocytopenia was Grade 3 or 4 in patients who received Pom + LD-Dex and who received HD-Dex. In Pom + LD-Dex treated patients, thrombocytopenia was serious, and led to dose reduction, to dose interruption and to treatment discontinuation (see section 4.4 and section 4.6).

Infection

Infection was the most common non haematological toxicity; it occurred in patients who received Pom + LD-Dex, and patients who received HD-Dex. Approximately half of those infections were Grade 3 or 4; in Pom + LD-Dex-treated patients and in patients who received HD-Dex.

In Pom + LD-Dex treated patients, pneumonia and upper respiratory tract infections were the most commonly reported infections with reported infections being serious and fatal infections (Grade 5) occurring in treated patients. In Pom + LD-Dex treated patients infections led to dose discontinuation, to treatment interruption, and to a dose reduction.

Thromboembolic events:

Venous embolic or thrombotic events (VTE) occurred in patients who received Pom + LD-Dex, and patients who received HD-Dex. Grade 3 or 4 reactions occurred in patients who received Pom + LD-Dex, and no

patients who received HD-Dex. In Pom + LD-Dex treated patients, VTE was reported as serious in patients, no fatal reactions were reported in clinical studies, and VTE was not associated with dose discontinuation. Anticoagulation therapy (unless contraindicated) is recommended (see section 4.2).

Peripheral neuropathy:

Patients with ongoing peripheral neuropathy ≥ Grade 2 were excluded from clinical studies. Peripheral neuropathy, mostly Grade 1 or 2 occurred in patients who received Pom + LD-Dex, and patients who received HD-Dex. Grade 3 or 4 reactions occurred in patients who received Pom + LD-Dex and in patients who received HD-Dex. In patients treated with Pom + LD-Dex, no peripheral neuropathy reactions were reported to have been serious in clinical trials and peripheral neuropathy led to dose discontinuation (see section 4.4 and section 4.6).

Haemorrhage:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

For any information about this medicine, please contact the local representative of the Holder of Certificate of Registration: Dr. Reddy's Laboratories (Pty) Ltd. Tel: +27 11 324 2100

4.9 Overdose

Adverse events will be an exaggeration of the side effects (see section 4.8). Treatment should be symptomatic and supportive. It is unknown whether pomalidomide or its metabolites are dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A.32. Other substances or agents.

Pharmacotherapeutic group: Other substances or agents; 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 synergizes 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 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.

Pomalidomide pro-erythropoietic activities were demonstrated in $CD34^+$ haematopoietic stem cells induced to differentiate toward the erythroid phenotype. These activities were manifested as a delayed erythroid maturation, increased proliferation of immature erythroid cells, and induction of foetal haemoglobin (HbF) production.

5.2 Pharmacokinetic properties

Absorption

Pomalidomide is absorbed with a C_{max} occurring between 2 and 3 hours and is > 70 % absorbed following administration of single oral dose. The systemic exposure (AUC) of pomalidomide increases in an approximately dose proportional manner. Following multiple doses, pomalidomide has an accumulation ratio of 27 - 31 %.

Co-administration with a high-fat and high-calorie meal slows the rate of absorption, decreasing plasma C_{max} by ~25 %, but has minimal effect on the overall extent of absorption with an 8 % decrease in 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 subjects at a concentration of approximately 67 % of plasma level at 4 hours post-dose (~T_{max}) after 4 days of once daily dosing at 4 mg. *In vitro* binding of pomalidomide enantiomers to proteins in human plasma ranges from 12 % to 44 % and is not concentration dependent.

Metabolism

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

Pomalidomide is eliminated in humans via multiple pathways including CYP-mediated metabolism, non-CYP dependent hydrolysis, and excretion of unchanged agent. The predominant metabolic pathways of excreted radioactivity are hydroxylation with subsequent glucuronidation, or hydrolysis. *In vitro*, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6.

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 exposure to pomalidomide by 104 % with a 90 % confidence interval [88 % to 122 %] compared to pomalidomide plus ketoconazole. If strong inhibitors of CYP1A2 are co-administered with pomalidomide, reduce the pomalidomide dose by 50 % for patients with multiple myeloma (based on the recommended starting doses) (see section 4.2).

Co-administration of multiple doses of 4 mg pomalidomide with 20 mg to 40 mg of 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.

Pomalidomide is a substrate of P-glycoprotein *in vitro*, but this did not appear to limit its absorption in humans, where at least 73 % of the substance was absorbed. Co-administration of pomalidomide with the

P-gp inhibitor ketoconazole had no clinically relevant effect on exposure to pomalidomide, therefore based on this, clinically relevant drug-drug interactions are not anticipated when pomalidomide is coadministered with inhibitors of P-glycoprotein.

Based on *in vitro* data, pomalidomide is not an inhibitor or inducer of cytochrome P-450 isoenzymes and does not inhibit P-glycoprotein, or other studied transporters. Clinically relevant drug-drug interactions are not anticipated when pomalidomide is co-administered with substrates of these pathways.

Elimination

Pomalidomide is eliminated with a median plasma half-life of approximately 9,5 hours in healthy subjects and approximately 7,5 hours in patients with multiple myeloma. Pomalidomide has a mean total body clearance (CL/F) of 7-10 L/hr.

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

Pomalidomide is extensively metabolised prior to elimination, 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).

Special Populations

Elderly

In patients aged 61 to 82, the mean pharmacokinetic parameters of AUC (0-∞) and C_{max} were generally similar to younger subjects.

Renal impairment

Population pharmacokinetic analyses showed that the pomalidomide pharmacokinetic parameters were not remarkably affected in renal impaired patients (defined by creatinine clearance or estimated glomerular filtration rate [eGFR]) relative to patients with normal renal function (CrCl ≥ 60 mL/minute).

Mean normalized AUC exposure to pomalidomide was 98,2 % with a 90 % confidence interval [77,4 % to

120,6 %] in moderate renal impairment patients (eGFR ≥ 30 to ≤ 45mL/minute/1,73 m2) relative to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2 % with a 90 % confidence interval [79,7 % to 127,0 %] in severe renal impairment patients not requiring dialysis (CrCl < 30 or eGFR < 30 mL/minute/1,73 m2) relative to patients with normal renal function. Mean normalized AUC exposure to pomalidomide increased by 35,8 % with a 90 % confidence interval [7,5 % to 70,0 %] in severe renal impairment patients requiring dialysis (CrCl < 30mL/minute requiring dialysis) relative 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 hepatic impaired patients (defined by Child-Pugh criteria) relative to healthy subjects. Mean exposure to pomalidomide increased by 51 % with a 90 % confidence interval [9 % to 110 %] in mildly hepatic impaired patients relative to healthy subjects. Mean exposure to pomalidomide increased by 58 % with a 90 % confidence interval [13 % to 119 %] in moderately hepatic impaired patients relative to healthy subjects. Mean exposure to pomalidomide increased by 72 % with a 90 % confidence interval [24 % to 138 %] in severely hepatic impaired patients relative to healthy subjects. The mean increases in exposure to pomalidomide in each of these hepatic impairment groups are not of a magnitude for which adjustments in schedule or dose are required.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous Lactose NF

Pregelatinized starch NF

Sodium stearyl fumarate NF

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

POMARZA 1 / 2 / 3 / 4 – pack size of 21's: HDPE container 75 cc with a CR Plastic cap with Pulp Liners, 33 mm

POMARZA 1 – pack size of 100's: HDPE container 75 cc with a CR Plastic cap with Pulp Liners, 33 mm

POMARZA 2 / 3 / 4 – pack size of 100's: HDPE container 100 cc with a CR Plastic cap with Pulp Liners, 38 mm

POMARZA 1 / 2 / 3 / 4 – pack size of 10's and 21's: Aluminium foil paper backed peel push, plain and cold formable foil

Not all strengths and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Capsules should not be opened or crushed. If powder from POMARZA 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block C, Woodmead North Office Park,

54 Maxwell Drive,

Woodmead, Sandton,

Gauteng,

2191

8. REGISTRATION NUMBERS

POMARZA 1: 59/32/0092

POMARZA 2: 59/32/0093

POMARZA 3: 59/32/0094

POMARZA 4: 59/32/0095

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03 February 2026

10. DATE OF REVISION OF TEXT