Professional Information For:

POMALIDOMIDE CIPLA Capsules

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

POMALIDOMIDE 1 mg CIPLA (hard capsules)

POMALIDOMIDE 2 mg CIPLA (hard capsules)

POMALIDOMIDE 3 mg CIPLA (hard capsules)

POMALIDOMIDE 4 mg CIPLA (hard capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

POMALIDOMIDE 1 mg CIPLA: Each hard capsule contains 1 mg of pomalidomide.

POMALIDOMIDE 2 mg CIPLA: Each hard capsule contains 2 mg of pomalidomide.

POMALIDOMIDE 3 mg CIPLA: Each hard capsule contains 3 mg of pomalidomide.

POMALIDOMIDE 4 mg CIPLA: Each hard capsule contains 4 mg of pomalidomide.

Contains sugar:

(Isomalt 25,1 mg/ 1 mg capsules; isomalt 50,2 mg/ 2 mg capsules; isomalt 75,3 mg/ 3 mg capsules and isomalt 100,4 mg/ 4 mg capsules).

For the full list of excipients, see **section 6.1**.

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.

If Pomalldomide 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 POMALIDOMIDE CIPLA AS NEGLIGIBLE AS POSSIBLE, POMALIDOMIDE CIPLA IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION RISK MANAGEMENT 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 RESTRICTED DISTRIBUTION RISK MANAGEMENT PROGRAM.

3. PHARMACEUTICAL FORM

Hard gelatin capsules.

POMALIDOMIDE 1 mg CIPLA

Yellow opaque cap and yellow opaque body, capsule shell size No. 4 imprinted in black ink with “LP” on the cap and “664” on the body and containing yellow granular powder.

POMALIDOMIDE 2 mg CIPLA

Orange opaque cap and orange opaque body, capsule shell size No. 3 imprinted in black ink with “LP” on the cap and “665” on the body and containing yellow granular powder.

POMALIDOMIDE 3 mg CIPLA

Light green opaque cap and light green opaque body, capsule shell size No. 2 imprinted in black ink with “LP” on the cap and “690” on the body and containing yellow granular powder.

POMALIDOMIDE 4 mg CIPLA

Blue opaque cap and blue opaque body, capsule shell size No. 2 imprinted in black ink with “LP” on the cap and “667” on the body and containing yellow granular powder.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

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

Posology

The recommended starting dose of POMALIDOMIDE CIPLA is 4 mg/day taken orally on Days 1 to 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.

POMALIDOMIDE CIPLA dose modification or interruption

Instructions for dose interruptions or reductions for POMALIDOMIDE CIPLA related to haematologic adverse reactions are outlined in the table below:

Dose modification instructions for POMALIDOMIDE CIPLA for haematologic toxicities:

Toxicity	**Dose modification**
Neutropenia ANC* < 500/µL or febrile neutropenia (fever ≥ 38,5 °C and ANC < 1,000/ µL)	Interrupt POMALIDOMIDE CIPLA treatment, follow CBC** weekly. Add G-CSF (at the discretion of the treating medical practitioner)
ANC* return to ≥ 500/µL	Resume POMALIDOMIDE CIPLA treatment at 3 mg daily one dose level lower than previous dose.
For each subsequent drop < 500/µL	Interrupt POMALIDOMIDE CIPLA treatment.
Return to ≥ 500/µL	Resume POMALIDOMIDE CIPLA treatment at 1 mg less than the previous dose.
Thrombocytopenia Platelet count < 25 000/µL	Interrupt POMALIDOMIDE CIPLA treatment, follow CBC** weekly.
Platelet count return to > 50 000/µL	Resume POMALIDOMIDE CIPLA treatment at 3 mg daily.
For each subsequent drop < 25 000/µL	Interrupt POMALIDOMIDE CIPLA treatment.
Platelet count return to ≥ 50 000/µL	Resume POMALIDOMIDE CIPLA treatment at 1 mg less than the previous dose.

*ANC – Absolute Neutrophil Count; **CBC – Complete Blood Count.

To initiate a new cycle of POMALIDOMIDE CIPLA, the neutrophil count must be ≥ 500/µL, the plateiet count must be ≥ 50 000/µL.

For other Grade 3/4 toxicities judged to be related to POMALIDOMIDE CIPLA, 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 POMALIDOMIDE CIPLA should be discontinued.

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 medicines 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.

Dose reduction levels (≤ 75 years of age):

- Starting dose of dexamethasone is 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 of dexamethasone is 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.

SPECIAL POPULATIONS

Elderly population

No dose adjustment is required for POMALIDOMIDE CIPLA.

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.

Renal impairment

Patients with renal impairment should be carefully monitored for adverse reactions. POMALIDOMIDE CIPLA should be avoided in patients with severe renal impairment (creatinine clearance < 30 mL/min/1, 75 m^2) and in patients with a serum creatinine concentration greater than 3,0mg/dL.

Hepatic impairment

POMALIDOMIDE CIPLA should be avoided in patients with serum billrubin greater than 2,0 mg/dL and AST or ALT greater than 3,0 mg/dL X U.L.N.

Paediatric population

No data are available on administration of POMALIDOMIDE CIPLA to paediatric or adolescent patients (< 18 years of age).

Method of administration

Oral use.

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

4.3. Contraindications

POMALIDOMIDE CIPLA is contraindicated for the following:

- Hypersensitivity to pomalidomide or any of the excipients listed in **section 6.1**.
- Pregnancy and breastfeeding (see **section 4.6**).
- Women of childbearing potential, except when all the conditions for pregnancy prevention programme have been 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

Teratogenicity

Pregnancy warning

POMALIDOMIDE CIPLA is contraindicated 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.

The conditions of the Risk Management Program 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 amenorrhoeic for ≥ 1 year (amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential)
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy

- XY genotype, Turner syndrome, uterine agenesis.

Counselling

For women of childbearing potential, POMALIDOMIDE CIPLA is contraindicated unless all 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 woman of childbearing potential has amenorrhea, 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 CIPLA 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 sterilisation.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of POMALIDOMIDE CIPLA.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Risk Management Program, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.

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

- He understands the expected teratogenic risk if engaged in sexual activity with a pregnant woman or woman of childbearing potential.
- He understands the need for the use of a condom if engaged in sexual activity with 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 CIPLA or 7 days after he has stopped taking POMALIDOMIDE CIPLA, 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

Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy including dose interruptions, and until 4 weeks after POMALIDOMIDE CIPLA 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 implant, levonorgestrel-releasing intrauterine system (IUS), medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills(e.g. desogestrel))
- Tubal sterilisation
- Partner vasectomy.

Effective methods:

- Male condom
- Daphragm
- Cervical cap.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking POMALIDOMIDE CIPLA and dexamethasone, combined oral contraceptive pills are not recommended (see **section 4.5**). If a patient is currently using combined oral contraception the patient should switch to two 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 50 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 CIPLA to women of childbearing potential should occur within 7 days of last pregnancy test.

Prior to starting treatment

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

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 within 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 POMALIDOMIDE CIPLA, 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 POMALIDOMIDE CIPLA.

Additional precautions

Patients should be instructed never to give POMALIDOMIDE CIPLA 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 4 weeks following discontinuation of POMALIDOMIDE CIPLA.

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, educational material will be provided to health care professionals to reinforce the warnings about the expected teratogenicity of POMALIDOMIDE CIPLA, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. Full patient information about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Risk Management Program should be given by the medical practitioner to women of childbearing potential and, as appropriate, to male patients.

Other special warnings and precautions for use:

Haematological events

Patients should be monitored for haematological adverse reactions, 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**). 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 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. Anticoagulation 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. The use of erythropoietic medicines carries a risk of thrombotic events including thromboembolism. Therefore, erythropoietic medicines, as well as other medicines that may increase the risk of thromboembolic events, should be used with caution.

Thyroid disorders

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 treating patients with ongoing ≥ Grade 2 peripheral neuropathy, with POMALIDOMIDE CIPLA.

Significant cardiac dysfunction

Appropriate caution should be exercised when considering the treatment of patients with pre-existing cardiac disease or cardiac risk factors with POMALIDOMIDE CIPLA, 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**). 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 severe skin reactions

Angioedema, anaphylactic reaction and serious dermatologic reactions including Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (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 CIPLA 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 may be at higher risk of hypersensitivity reactions and should not receive POMALIDOMIDE CIPLA. POMALIDOMIDE CIPLA interruption or discontinuation should be considered for Grade 2 – 3 skin rash. POMALIDOMIDE CIPLA must be discontinued permanently for angioedema and anaphylactic reaction.

Dizziness and confusion

Patients must avoid situations where dizziness or confusion may be a problem and not 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. POMALIDOMIDE CIPLA should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. POMALIDOMIDE CIPLA 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 CIPLA and as clinically indicated thereafter.

Infections

Hepatitis B virus status should be established before initiating treatment with POMALIDOMIDE CIPLA. For patients who test positive for HBV infection, consultation with a medical practitioner with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when POMALIDOMIDE CIPLA 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. Medical practitioners 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 CIPLA must be permanently discontinued.

POMALIDOMIDE CIPLA containsa isomalt, and may have a laxative effect. Patients with rare hereditary problems of fructose intolerance should not take POMALIDOMIDE CIPLA.

4.5. Interaction with other medicines and other forms of interaction

Effect of POMALIDOMIDE CIPLA on other medicines

POMALIDOMIDE CIPLA 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 medicine interactions, including the potential impact of POMALIDOMIDE CIPLA on the pharmacokinetics of combined oral contraceptives, has not been evaluated clinically.

Effect of other medicines on POMALIDOMIDE CIPLA

POMALIDOMIDE CIPLA is partly metabolised by CYP1A2 and CYP3A4/5. It is also a substrate for P-glycoprotein. Co-administration of POMALIDOMIDE CIPLA with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, does not have clinically relevant effect on exposure to POMALIDOMIDE CIPLA.

If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with POMALIDOMIDE CIPLA, reduce the dose of POMALIDOMIDE CIPLA by 50 %.

Dexamethasone

Co-administration of multiple doses of up to 4 mg POMALIDOMIDE CIPLA with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of several CYP enzymes including CYP3A) to patients with multiple myeloma does not have an effect on the pharmacokinetics of pomalidomide compared with pomlidomide given 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

Women of childbearing potential should use two effective methods of contraception. If pregnancy occurs in a woman treated with POMALIDOMIDE CIPLA, 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 POMALIDOMIDE CIPLA, it is recommended to refer the female partner to a medical practitioner specialised or experienced in teratology for evaluation and advice.

Males

Pomalidomide is present in human semen. As a precaution, all male patients taking POMALIDOMIDE CIPLA 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 **sections 4.3** and **4.4**).

Pregnancy

POMALIDOMIDE CIPLA is contraindicated during pregnancy and in women of childbearing potential, unless all the conditions for pregnancy prevention have been met, see **section 4.3** and **section 4.4**.

Breastfeeding

Breastfeeding of infants is contraindicated in mothers taking POMALIDOMIDE CIPLA, see **section 4.3.**

4.7. Effects on ability to drive and use machines

POMALIDOMIDE CIPLA 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, judgement and/or sound coordination and vision.

4.8. Undesirable effects

a) Summary of the safety profile

The most frequently 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 in 12,3 % of patients and venous embolic or thrombotic (VTE) adverse reactions were reported in 3,3 % of patients. The most frequently 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 frequently reported serious adverse reaction was pneumonia. Other serious adverse reactions reported included febrile neutropenia, neutropenia, thrombocytopenia and VTE adverse reactions.

b) Tabulated list of adverse reactions (ADR`s)

Below: Averse reactions reported in patients treated with pomalidomde in combination with dexamethasone, listed by system organ class:

System Organ Class/ Preferred Term	All ADRs/Frequency	Grade 3−4 ADRs/Frequency
Infections and infestations	**Frequent** Pneumonia (bacterial, viral and fungal infections, including opportunistic	**Frequent** Neutropenic sepsis, pneumonia (bacterial, viral and fungal infections,

	infections), neutropenic sepsis, bronchopneumonia, bronchitis, respiratory tract infection, upper respiratory tract infection, nasopharyngitis, herpes zoster, septic shock, *Clostridium difficile* colitis, lower respiratory tract infection, lung infection, influenza, bronchiolitis, urinary tract infection. **Frequency unknown** Hepatitis B reactivation	including opportunistic infections), bronchopneumonia, respiratory tract infection, upper respiratory tract infection, septic shock, *Clostridium difficile* colitis, lower respiratory tract infection, lung infection, influenza, bronchiolitis, urinary tract infection. **Less Frequent** Bronchitis, herpes zoster **Frequency unknown** Hepatitis B reactivation
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Less Frequent** Basal cell carcinoma of the skin, squamous cell carcinoma of the skin	**Less Frequent** Basal cell carcinoma of the skin, squamous cell carcinoma of the skin
Blood and lymphatic system disorders	**Frequent** Neutropenia, thrombocytopenia, leucopenia, anaemia, febrile neutropenia, lymphopenia, pancytopenia.	**Frequent** Neutropenia, thrombocytopenia, anaemia, febrile neutropenia, leucopenia, lymphopenia, pancytopenia.
Immune system disorders	**Frequent** Angioedema, urticaria **Frequency unknown** Anaphylactic reaction Solid organ transplant rejection.	**Less Frequent** Angioedema, urticaria **Frequency unknown** Anaphylactic reaction.
Endocrine disorders	**Less Frequent** Hypothyroidism.	
Metabolism and nutrition disorders	**Frequent** Decreased appetite, hyperkalaemia, hyponatraemia, hyperuricaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypophosphataemia. **Less Frequent** Tumour lysis syndrome.	**Frequent** Hyperkalaemia, hyponatraemia, hyperuricaemia, hypokalaemia, hyperglycaemia, hypomagnesaemia, hypocalcaemia, hypophosphataemia. **Less Frequent** Decreased appetite, tumour lysis syndrome.

Psychiatric disorders	**Frequent** Confusional state, insomnia, depression.	**Frequent** Confusional state, insomnia, depression.
Nervous system disorders	**Frequent** Depressed level of consciousness, peripheral sensory neuropathy, dizziness, tremor, intracranial hemorrrhage, syncope, peripheral sensorimotor neuropathy, paraesthesia, dysgeusia. **Less Frequent** Cerebrovascular accident.	**Frequent** Depressed level of consciousness, syncope, peripheral sensory neuropathy, peripheral sensorimotor neuropathy. **Less Frequent** Peripheral sensory neuropathy, dizziness, tremor, cerebrovascular accident, intracranial haemorage.
Eye disorders	**Frequent** Cataract.	**Frequent** Cataract.
Ear and labyrinth disorders	**Frequent** Vertigo	**Frequent** Vertigo.
Cardiac disorders	**Frequent** Cardiac failure, atrial fibrillation, myocardial infarction.	**Frequent** Cardiac failure, atrial fibrillation **Less Frequent** Myocardial infarction.
Vascular disorders	**Frequent** Deep vein thrombosis, hypotension, hypertension.	**Less Frequent** Hypotension, hypertension. **Less Frequent** Deep vein thrombosis.
Respiratory, thoracic and mediastinal disorders	**Frequent** Dyspnoea, cough, pulmonary embolism, epistaxis, interstitial lung disease.	**Frequent** Dyspnoea. **Less Frequent** Pulmonary embolism, cough, epistaxis, interstitial lung disease.
Gastrointestinal disorders	**Frequent** Diarrhoea, nausea, constipation, vomiting.	**Frequent** Diarrhoea, vomiting, constipation, abdominal pain.

	gastrointestinal haemorrhage, abdominal pain, abdominal pain upper, stomatitis, dry mouth, abdominal distension.	**Less Frequent** Nausea, gastrointestinal haemorrhage, abdominal pain upper, stomatitis, nausea, abdominal distension.
Hepatobiliary disorders	**Less Frequent** Hyperbilirubinaemia, hepatitis	**Less Frequent** Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	**Frequent** Rash, pruritus. **Frequency unknown** Drug Reaction with Eosinophilia and Systemic Symptoms, Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome.	**Frequent** Rash. **Frequency unknown** Drug Reaction with Eosinophilia and Systemic Symptoms, Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome.
Musculoskeletal and connective tissue disorders	**Frequent** Bone pain, muscle spasms, muscular weakness, back pain.	**Frequent** Bone pain, muscular weakness. **Less Frequent** Muscle spasms, bone pain.
Renal and urinary disorders	**Frequent** Renal failure, urinary retention, acute kidney injury, chronic kidney injury.	**Frequent** Renal failure, acute kidney injury, chronic kidney injury. **Less Frequent** Urinary retention
Reproductive system and breast disorders	**Frequent** Pelvic pain.	**Frequent** Pelvic pain.
General disorders and administration site conditions	**Frequent** Fatigue, pyrexia, oedema peripheral, non-cardiac chest pain, oedema.	**Frequent** Fatigue, pyrexia, oedema peripheral, non-cardiac chest pain, oedema.
Investigations	**Frequent** Decreased neutrophil count, decreased white blood cell count, decreased platelet count, increased alanine aminotransferase, increased blood uric acid.	**Frequent** Decreased neutrophil count, decreased white blood cell count, decreased platelet count, increased alanine aminotransferase,

		Less Frequent Increased blood uric acid.
Injury, poisoning and procedural complications	**Frequent** Fall	**Less Frequent** Fall

c) Description of selected adverse reactions

Teratogenicity

POMALIDOMIDE CIPLA is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects.

If POMALIDOMIDE CIPLA is taken during pregnancy, a teratogenic effect of POMALIDOMIDE CIPLA in humans is expected (see **section 4.4**).

Neutropenia and thrombocytopenia

In patients receiving combination therapy with POMALIDOMIDE CIPLA, neutropenia and thrombocytopenia do occur. Neutropenia does not lead to POMALIDOMIDE CIPLA discontinuation in any patient.

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

Infection

Infection is the most frequent non haematological toxicity in patients receiving combination therapy with POMALIDOMIDE CIPLA. Upper respiratory tract infection and pneumonia are the most frequently occurring infections. Fatal infections (Grade 5) do occur.

Thromboembolic events

Venous thromboembolic events (VTE) does occur in patients receiving combination therapy with POMALIDOMIDE CIPLA. Prophylaxis with acetylsalicylic acid (and other anticoagulants in high risk patients) is mandatory for all patients. Anticoagulation therapy (unless contraindicated) is recommended (see **section 4.4**).

Peripheral neuropathy

Peripheral neuropathy reaction does occur in patients receiving POMALIDOMIDE CIPLA (see **section 4.4**).

Haemorrhage

Haemorrhagic disorders have been reported with POMALIDOMIDE CIPLA, 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.

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 CIPLA. Patients with a history of severe rash associated with lenalidomide or thalidomide should not receive POMALIDOMIDE CIPLA (see **section 4.4**).

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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8 or drugsafetysa@cipla.com or telephone 080222 6662 (toll free)

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 not known whether pomalidomide or its metabolites are dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 32 Other – Immunosuppressants

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. 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 maximum plasma concentration (C_{max}) occurring between 2 and 3 hours and is at least 70 % 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 %.

Coadministration with a high-fat and high-calorie meal slows the rate of absorption, decreasing mean plasma C_{max} by approximately 25 %, 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 subjects at a concentration of approximately 67 % of plasma level at 4 hours post-dose (approximately 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.

Biotransformation

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.

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 mean exposure to pomalidomide by 104 % with a 90 % confidence interval [88 % to 122 %] compared to pomalidomide plus ketoconazole. If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, patients should be closely moitored for the occurrence of side effects.

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 co-administered witli inhibitors of P-glycoprotein.

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 approximately 7-10 L/hr.

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).

Pharmacokinetics in children, elderly, patients with renal and hepatic impairment:

No studies have been performed with pomalidomide.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Isomalt (E 953)

Pregelatinized starch

Sodium stearyl fumarate

Composition of empty **1 mg** capsule shell:

Gelatin

Titanium dioxide (E171)

Yellow iron oxide (E172)

Composition of empty **2 mg** capsule shell:

Gelatin

Titanium dioxide (E171)

Yellow iron oxide (E172)

Red iron oxide (E172)

Composition of empty **3 mg** capsule shell:

Gelatin

Titanium dioxide (E171)

Brilliant blue FCF-FD&C Blue 1 (E133)

Composition of empty **4 mg** capsule shell:

Gelatin

Titanium dioxide (E171)

FD&C Red #3 (E127)

Brilliant blue FCF-FD&C Blue 1 (E133)

Composition of printing ink:

Shellac

Dehydrated alcohol

Isopropyl alcohol

Butyl alcohol

Propylene glycol

Purified water

Strong ammonia solution

Potassium hydroxide

Black iron oxide (E172)

6.2. Incompatibilities

Not applicable

6.3 Shelf Life

36 months, stored at or below 30 °C

6.4 Special precautions for storage

Store at or below 30 °C.

6.5. Nature and contents of container

POMALIDOMIDE CIPLA is packed in transparent PVC/Aclar-aluminum blisters and aluminum-aluminum blisters.

Each pack contains 21 capsules.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

POMALIDOMIDE 1 mg CIPLA: 56/32/0540

POMALIDOMIDE 2 mg CIPLA: 56/32/0541

POMALIDOMIDE 3 mg CIPLA: 56/32/0542

POMALIDOMIDE 4 mg CIPLA: 56/32/0543

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 July 2023

Date of latest renewal: TBC

10. DATE OF REVISION OF THE TEXT