PROFESSIONAL INFORMATION FOR POMYLO

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

POMYLO 1 mg hard capsule.

POMYLO 2 mg hard capsule.

POMYLO 3 mg hard capsule.

POMYLO 4 mg hard capsule.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **POMYLO 1 mg** hard capsule contains 1 mg pomalidomide.

Contains sugar (Mannitol, 41 mg).

Each **POMYLO 2 mg** hard capsule contains 2 mg pomalidomide.

Contains sugar (Mannitol, 82 mg).

Each **POMYLO 3 mg** hard capsule contains 3 mg pomalidomide.

Contains sugar (Mannitol, 60 mg).

Each **POMYLO 4 mg** hard capsule contains 4 mg pomalidomide.

Contains sugar (Mannitol, 80 mg).

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsule.

POMYLO 1 mg: Dark blue cap and yellow body size “4” capsules printed

with “NAT” with white ink on cap and “1 mg” with black ink on body of the capsule,

contains light yellow to yellow coloured powder.

POMYLO 2 mg: Dark blue cap and orange body size “2” capsules printed with “NAT” with white ink on cap and “2 mg” with white ink on body of the capsule, contains light yellow to yellow coloured powder.

POMYLO 3 mg: Dark blue cap and green body size “2” capsules printed with “NAT” with white ink on cap and “3 mg” with white ink on body of the capsule, contains light yellow to yellow coloured powder.

POMYLO 4 mg: Dark blue cap and blue body size “2” capsules printed with “NAT” with white ink on cap and “4 mg” with white ink on body of the capsule, contains light yellow to yellow coloured powder.

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 POMYLO AS NEGLIGIBLE AS POSSIBLE,

POMYLO IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME. THIS PROGRAMME IS CALLED THE ACTIVE RISK MANAGEMENT PROGRAM.

UNDER THIS RESTRICTED DISTRIBUTION PROGRAMME, ONLY PRESCRIBERS 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 ACTIVE RISK MANAGEMENT PROGRAM.

WARNING:

VENOUS THROMBO EMBOLISM:

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

POMYLO in combination with dexamethasone is indicated for 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 medical practitioner experienced in the management of multiple myeloma.

Dosage:

The recommended starting dose of **POMYLO** 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.

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POMYLO dose modification or interruption:

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

Dose modification instructions for POMYLO for haematologic toxicities:

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

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

PROFESSIONAL INFORMATION FOR POMYLO

To initiate a new cycle of **POMYLO** 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 **POMYLO**, 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.

Dexamethasone dose modification instructions:

Dexamethasone dose reduction levels:

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 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

	agents 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.

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 **POMYLO**.

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

A study in subjects with renal impairment has not been conducted with **POMYLO.**

Patients with moderate or severe renal impairment (creatinine clearance < 45 mL/min) were excluded from clinical studies. Patients with renal impairment should

be carefully monitored for adverse reactions. **POMYLO** 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 3,0 mg/dL.

Hepatic impairment

A study in subject with hepatic impairment has not been conducted with **POMYLO.** Patients with serum total bilirubin > 2,0 mg/dL were excluded from clinical studies. **POMYLO** should be avoided in patients with serum bilirubin greater than 2,0 mg/dL and AST or ALT greater than 3,0 mg/dL x ULN.

Paediatric population:

No data are available on administration of **POMYLO** to paediatric or adolescent subjects (< 18 years of age).

Method of administration:

Oral use.

POMYLO should be taken at the same time each day. The capsules should not be opened, broken or chewed. This medicine should be swallowed, preferably with water, with or without food.

4.3 Contraindications

- Hypersensitivity to **POMYLO** (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).

PROFESSIONAL INFORMATION FOR POMYLO

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. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. If **POMYLO** is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected.

The conditions of the Active 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 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 ≥ 1 year*.
- Premature ovarian failure confirmed by a specialist gynaecologist.
- Previous bilateral salpingo-oophorectomy, or hysterectomy.
- XY genotype, Turner syndrome, uterine agenesis.

* Amenorrhoea following cancer therapy or during breastfeeding does not rule out childbearing potential.

Counselling:

For women of childbearing potential, **POMYLO** 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 female 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 **POMYLO** 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 **POMYLO**.

The prescriber must ensure that for females of childbearing potential:

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

For male patients taking **POMYLO**, pharmacokinetic data has demonstrated that pomalidomide is present in human semen.
As a precaution, all male patients taking **POMYLO** 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 **POMYLO** or for 4 weeks after he has stopped taking **POMYLO**, 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 **POMYLO** 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 of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended (see also section 4.5). If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during 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:

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 50 IU/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 **POMYLO** 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 **POMYLO** 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 **POMYLO.**

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 **POMYLO**, 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 **POMYLO**.

Additional precautions:

Patients should be instructed never to give **POMYLO** 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 **POMYLO**.

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).

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Educational materials

In order to assist patients in avoiding fetal exposure to pomalidomide, educational material will be provided to healthcare providers to reinforce the warnings about the expected teratogenicity of **POMYLO**, 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 Active Risk Management Program should be given by the medical practitioner to females of childbearing potential and, as appropriate, to male patients.

Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of pomalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens (see section 4.2), and prescriptions for all other patients can be for a maximum duration of 12 weeks.

Haematological events:

Neutropenia was the most frequently reported Grade 3/ 4 haematological adverse reaction (AR) in patients with relapsed/refractory multiple myeloma, followed by anaemia and thrombocytopenia. Monitor patients for haematological toxicities, especially neutropenia. Monitor complete blood counts 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 **POMYLO** 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 healthcare professionals 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 carefully after assessment of an 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

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

Peripheral neuropathy

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

Significant cardiac dysfunction

Patients with significant cardiac dysfunction (congestive heart failure [NY Heart Association Class Ill or IV]; myocardial infarction within 12 months of starting study; unstable or poorly controlled angina pectoris) were excluded from clinical studies with pomalidomide. Cardiac events, including congestive cardiac failure, pulmonary oedema and atrial fibrillation (see

section 4.8), have been reported, mainly in patients with pre-existing cardiac disease or cardiac risk factors. Appropriate caution should be exercised when considering the treatment of such patients with pomalidomide, including periodic monitoring for signs or symptoms of cardiac events.

Tumour lysis syndrome:

Tumour lysis syndrome may occur. 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 **POMYLO** (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 severe 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. **POMYLO** 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 pomalidomide were excluded from clinical studies. Such patients may be at higher risk of hypersensitivity reactions and should not receive **POMYLO**. Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued permanently for angioedema and anaphylactic reaction.

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Pulmonary hypertension:

Cases of pulmonary hypertension, some fatal, have been reported in patients treated with pomalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during pomalidomide therapy.

Dizziness and confusion:

Confusion, fatigue, depressed level of consciousness and dizziness have been reported with the use of pomalidomide. Patients must avoid situations where dizziness or confusion may be a problem and should 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.
POMYLO should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated.
POMYLO 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 **POMYLO** and as clinically indicated thereafter.

Infections

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Reactivation of hepatitis B has been reported in patients receiving pomalidomide in combination with dexamethasone who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure, resulting in discontinuation of pomalidomide. Hepatitis B virus status should be established before initiating treatment with pomalidomide. For patients who test positive for HBV infection, consultation with a medical practitioner 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. 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 must be permanently discontinued.

Excipient warning:

POMYLO contains less than 1 mmol sodium (23 mg) per capsule,

that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Effect of POMYLO on other medicines:

POMYLO 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 **POMYLO** on exposure of oral contraceptives, has not been evaluated clinically.

Effect of other medicines on POMYLO:

Pomalidomide is partly metabolised by CYP1 A2 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. Co-administration of fluvoxamine alone with pomalidomide increased mean exposure to pomalidomide by 125 % with a 90% confidence interval [98 % to 157 %] compared to pomalidomide alone. If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with **POMYLO**, patients should be closely monitored for the occurrence of side effects.

Dexamethasone:

Co-administration of multiple doses of 4 mg **POMYLO** 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 **POMYLO**, 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 **POMYLO**, 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 **POMYLO** 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:

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

Pomalidomide was found to be teratogenic in embryo-foetal development toxicity studies in rats and rabbits. Pomalidomide crosses the placenta and was detected in foetal blood following administration to pregnant rabbits.

Breastfeeding:

Breastfeeding of infants is contraindicated in mothers taking **POMYLO**.

Pomalidomide was detected in milk of lactating rats following administration to the

mother.

Fertility:

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

4.7 Effects on ability to drive and use machines

POMYLO 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.

4.8 Undesirable effects

a. Summary of the safety profile

The 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 peripheral oedema; and in infections and infestations including pneumonia. Peripheral neuropathy and venous embolic or thrombotic (VTE) adverse reactions were also reported.

The frequently reported serious adverse reaction was pneumonia. Other serious adverse reactions reported included febrile neutropenia, neutropenia, thrombocytopenia and VTE adverse reactions.

System Organ Class:	**Frequency:**	**Side effects**
Infections and Infestations	Frequent	Pneumonia (bacterial, viral and fungal infections, including opportunistic infections), neutropenic sepsis, septic shock,

		Clostridium difficile colitis, influenza, bronchiolitis, urinary tract infection, bronchopneumonia, bronchitis respiratory tract infection, upper respiratory tract infections, nasopharyngitis, herpes zoster
	Frequency unknown	Hepatitis B reactivation
Neoplasms benign, malignant and unspecified (including cysts and polyps)	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, pancytopenia*
Immune system disorders	Frequent	Angioedema*, urticaria*
Metabolism and nutrition disorders	Frequent	Decreased appetite, hyperkalaemia, hyponatraemia, hyperuricaemia*, hypokalaemia, hyperglycaemia, hypomagnaesaemia, hypocalcaemia, hypophosphataemia, hypercalcaemia
	Less frequent	Tumour lysis syndrome*
Psychiatric	Frequent	Confusional state, insomnia,

disorders		depression
Nervous system disorders	Frequent Less frequent	Depressed level of consciousness, peripheral sensory neuropathy, dizziness, tremor, intracranial haemorrhage*, paraesthesia, dysgeusia, syncope Cerebrovascular accident*
Ear and labyrinth disorders	Frequent	Vertigo
Eye disorders	Frequent	Cataract
Vascular disorders	Frequent	Deep vein thrombosis, hypotension, hypertension
Cardiac disorders	Frequent	Cardia failure*, atrial fibrillation*, myocardial infarction*
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Dyspnoea, cough, pulmonary embolism, epistaxis*, interstitial lung disease* Pulmonary hypertension
Gastrointestinal disorders	Frequent	Diarrhoea, nausea, constipation, vomiting, gastrointestinal haemorrhage, abdominal pain, stomatitis, dry mouth, abdominal distension
Hepato-biliary disorders	Less frequent	Hyperbilirubinaemia, hepatitis*
Skin and	Frequent	Rash, pruritus

subcutaneous tissue disorders	Frequency unknown	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome
Musculoskeletal, and connective tissue disorders	Frequent	Bone pain, muscle spasms, muscular weakness, back pain
Renal and urinary disorders	Frequent	Renal failure, urinary retention, acute kidney injury, chronic kidney injury
Reproductive system and breast disorders	Frequent	Pelvic pain
General disorders and administration site conditions	Frequent	Fatigue, pyrexia, peripheral oedema, non-cardiac chest pain
Investigations	Frequent	Decreased neutrophil count, decreased white blood cell count, decreased platelet count, increased alanine aminotransferase, increased blood uric acid*
Injury, poisoning and procedural complications	Frequent	Fall

* Identified from post marketing data.

Reporting of suspected adverse reactions:

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Reporting of 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.

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 unknow whether pomalidomide or its metabolites are dialysable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group and ATC code:

Other immunosuppressants/L04AX06

5.1 Pharmacodynamic Properties:

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 polyubiquitination 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 a 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 mean plasma C_{max} by approximately 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 (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.

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 CYP2C 19 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, patients should be closely monitored 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 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 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).

PROFESSIONAL INFORMATION FOR POMYLO

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

Capsule content:

Croscarmellose Sodium

Mannitol

Pregelatinized starch

Sodium stearyl fumarate

Capsule shell:

POMYLO 1 mg and POMYLO 3 mg:

Gelatine

FD&C Blue 2 (E132)

Iron oxide yellow (E172)

Titanium dioxide (E171)

POMYLO 2 mg:

Gelatine

FD&C Blue 2 (E132)

FD&C Red 3 (E127)

Iron oxide yellow (E172)

Titanium dioxide (E171)

POMYLO 4 mg:

Gelatine

FD&C Blue 2 (E132)

Titanium dioxide (E171)

PROFESSIONAL INFORMATION FOR POMYLO

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 30 °C.

6.5 Nature and contents of container

White HDPE bottle with child resistant cap.

Clear transparent PVC/Aclar film with plain aluminium foil blisters containing 7 hard capsules per blister strip. The blisters are packed into cartons.

Pack size: 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).

PROFESSIONAL INFORMATION FOR POMYLO

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

2 Waterford Mews

Waterford Place

7441

Century City

Cape Town

South Africa

8. REGISTRATION NUMBERS

POMYLO 1 mg: 56/32.2/0189

POMYLO 2 mg: 56/32.2/0190

POMYLO 3 mg: 56/32.2/0191

POMYLO 4 mg: 56/32.2/0192

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

27 June 2023