POMAXEL

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 POMAXEL AS NEGLIGIBLE AS POSSIBLE, POMAXEL IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME. THIS PROGRAMME IS CALLED THE EUROLAB PREGNANCY PROTECTION 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 EUROLAB PREGNANCY PROTECTION PROGRAMME.

WARNING:

VENOUS THROMBO EMBOLISM:

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

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

POMAXEL 1 mg capsules

POMAXEL 2 mg capsules

POMAXEL 3 mg capsules

POMAXEL 4 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

POMAXEL 1 mg capsules

Each **POMAXEL** capsule contains 1 mg of pomalidomide.

POMAXEL 2 mg capsules

Each **POMAXEL** capsule contains 2 mg of pomalidomide.

POMAXEL 3 mg capsules

Each **POMAXEL** capsule contains 3 mg of pomalidomide.

POMAXEL 4 mg capsules

Each **POMAXEL** capsule contains 4 mg of pomalidomide.

Excipients with known effect:

POMAXEL 1 mg capsules

POMAXEL contains 25,1 mg of sugar (isomalt) per capsule.

POMAXEL 2 mg capsules

POMAXEL contains 50,2 mg of sugar (isomalt) per capsule.

POMAXEL 3 mg capsules

POMAXEL contains 75,3 mg of sugar (isomalt) per capsule.

POMAXEL 4 mg capsules

POMAXEL contains 100,4 mg of sugar (isomalt) per capsule.

For the full list of excipients, see section 6.1.

POMAXEL contains sugar.

3 PHARMACEUTICAL FORM

POMAXEL 1 mg capsules

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.

POMAXEL 2 mg capsules

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.

POMAXEL 3 mg capsules

Powder blue opaque cap and powder blue 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.

POMAXEL 4 mg capsules

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

POMAXEL 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.

POMAXEL 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 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.

In combination with bortezomib and dexamethasone (PBd) - patients with relapsed or refractory multiple myeloma after at least one prior therapy including lenalidomide:

Recommended dosage:

The recommended starting dose of **POMAXEL** 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 below.

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

Treatment should 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.

POMAXEL dose modification or interruption:

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

Dose modification instructions for **POMAXEL** for haematologic toxicities:

Toxicity	Dose modification
Neutropenia • ANC < 500/µL or Febrile neutropenia (fever ≥ 38,5 °C and ANC < 1,000/µL) • Pd regiment: ANC return to ≥ 500/µL • PBd regimen: ANC return to ≥ 1000/µL	Interrupt **POMAXEL** treatment, follow CBC weekly. Add G-CSF (at the discretion of the treating medical practitioner). Resume **POMAXEL** at 3 mg daily.
• For each subsequent drop < 500/µL • Pd regimen: Return to ≥ 500/µL • PBd regimen: Return to ≥ 1000/µL	Interrupt **POMAXEL** treatment. Resume **POMAXEL** at 1 mg less than the previous dose.
Thrombocytopenia • Platelets < 25 000/µL • Platelets return to > 50 000/µL	Interrupt **POMAXEL** treatment, follow CBC weekly. Resume **POMAXEL** treatment at 3 mg daily.
• For each subsequent drop < 25 000/µL • Return to ≥ 50 000/µL	Interrupt **POMAXEL** treatment. Resume **POMAXEL** at 1 mg less than

	previous dose.

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

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

Pd regimen: To initiate a new cycle of **POMAXEL**, 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 **POMAXEL**, 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 **POMAXEL**, reduce the recommended starting **POMAXEL** 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 prescribing information.

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.

Discontinuation of POMAXEL

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

POMAXEL 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-120 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.

<u>Special populations</u>

Elderly population

No dose adjustment is required for **POMAXEL**.

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 greater 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 **POMAXEL** is required for patients with renal impairment. On haemodialysis days, patients should take their **POMAXEL** dose following haemodialysis.

Hepatic impairment

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

Paediatric population

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

In a Phase 1 single-arm, open-label, dose escalation study, the maximum tolerated dose (MTD) of pomalidomide in paediatric patients was determined to be 2,6 mg/m^2/day

administered orally on day 1 to day 21 of a repeated 28-day cycle. The MTD was administered in a Phase 2 study.

Efficacy was not demonstrated in a Phase 2 multicenter, open-label, parallel-group study conducted in 52 pomalidomide-treated paediatric patients, aged 4 to 18 years with recurrent or progressive high-grade glioma, medulloblastoma, ependymoma, or diffuse intrinsic pontine glioma (DIPG) with primary location in the CNS.

In the Phase 2 study, two patients in the high-grade glioma group (N=19) achieved either an OR (objective response) or an SD (stable disease) (one of these patients achieved a partial response [PR] and the other patient achieved an SD) which resulted in an OR and long-term SD rate of 10,5 % (95 % CI: 1,3, 33,1). One patient in the ependymoma group (N=9) maintained a long-term SD which resulted in an OR and long-term SD rate of 11,1 % (95 % CI: 0,3, 48,2). No confirmed OR or long-term SD was observed in either the diffuse intrinsic pontine glioma (DIPG) group (N=9) or medulloblastoma group (N=9). None of the 4 parallel groups assessed in this Phase 2 study met the primary endpoint of objective response or long-term stable disease rate.

The overall safety profile of pomalidomide in paediatric patients was consistent with the known safety profile in adults. Pharmacokinetic (PK) parameters were evaluated in an Integrated PK Analysis of the Phase 1 and Phase 2 studies and were found to have no significant difference to those observed in adult patients.

Method of administration

Oral use.

POMAXEL should be taken at the same time each day. The capsules should not be chewed, crushed or bitten. This medicine should be swallowed whole, preferably with water, with or without food.

4.3 Contraindications

- Hypersensitivity to the pomalidomide or to any of the excipients of **POMAXEL** listed in section 6.1.
- Pregnancy and lactation.
- Women of childbearing potential, unless all the conditions of the Eurolab Pregnancy Protection Programme are met (see sections 4.4 and 4.6).
- Male patients unable to follow or comply with the required contraceptive measures (see section 4.4).

For information on other medicinal products given in combination with **POMAXEL**, refer to the respective current Professional Information.

4.4 Special warnings and precautions for use

Teratogenicity

POMAXEL must not be taken during pregnancy, since a teratogenic effect is expected. Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening birth defects.

The conditions of the Eurolab Pregnancy Protection Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for women of non-childbearing potential

A female patient or a female partner of a male patient is considered of non-childbearing potential if she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 2 years (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, **POMAXEL** is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child.
- She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment.
- Even if a woman of childbearing potential has amenorrhoea, she must follow all the advice on effective contraception.
- She should be capable of complying with effective contraceptive measures.
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.
- She understands the need to commence the treatment as soon as pomalidomide is dispensed following a negative pregnancy test.
- She understands the need and accepts to undergo pregnancy testing at least every 4 weeks except in case of confirmed tubal sterilisation.
- She acknowledges that she understands the hazards and necessary precautions associated with the use of **POMAXEL.**

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Eurolab Pregnancy Protection Programme, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.

For male patients taking **POMAXEL**, pharmacokinetic data has demonstrated that pomalidomide is present in human semen during treatment. As a precaution and taking into account special populations with potentially prolonged elimination time such as hepatic impairment, all male patients taking **POMAXEL** must meet the following conditions:

- He understands the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.
- He understands the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception, throughout treatment duration and for 4 weeks, 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 **POMAXEL** or for 4 weeks after he has stopped taking **POMAXEL**, he should inform his treating doctor immediately and that it is recommended to refer the female partner to a doctor specialised or experienced in teratology for evaluation and advice.

<u>Contraception</u>

Women of childbearing potential must use two reliable methods of contraception for at least 4 weeks before therapy, during therapy, and until at least 4 weeks after **POMAXEL** therapy and even in case of dose interruption, unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:
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 sterilisation.
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses.

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 25 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of **POMAXEL** to women 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 **POMAXEL** 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 **POMAXEL**.

Follow-up and end of treatment

A medically supervised pregnancy test should be repeated at least every 4 weeks, including at least 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 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 **POMAXEL**, 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 **POMAXEL**.

Additional precautions

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

Patients should not donate blood during treatment (including during dose interruptions) and for 4 weeks following discontinuation of **POMAXEL**.

Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule (see section 6.6).

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to pomalidomide, the Marketing Authorisation Holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of **POMAXEL**, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The medical practitioner must inform the patient about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Eurolab Pregnancy Protection Programme to women 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 is the most frequently reported Grade 3 or 4 haematological adverse reaction in patients with relapsed/refractory multiple myeloma, followed by anaemia and thrombocytopenia. Patients should be monitored for haematological adverse reactions, especially neutropenia. Patients should be advised to report febrile episodes promptly. Doctors should observe patients for signs of bleeding including epistaxis, especially with use of concomitant medicinal products known to increase the risk of bleeding (see section 4.8). Complete blood counts should be monitored at baseline, weekly for the first 8 weeks and monthly thereafter. A dose modification may be required (see section 4.2). Patients may require use of blood product support and /or growth factors.

Thromboembolic events

Patients receiving **POMAXEL**, have developed venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) and arterial thrombotic events (myocardial infarction and cerebrovascular accident). Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Patients and doctors 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 anti-thrombotic therapy. The use of erythropoietic agents carries a risk of thrombotic events including thromboembolism. Therefore, erythropoietic agents, as well as other agents that may increase the risk of thromboembolic events, should be used with caution.

Thyroid disorders

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

Peripheral neuropathy

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

Significant cardiac dysfunction

Patients with significant cardiac dysfunction (congestive heart failure [NY Heart Association Class III or IV]; myocardial infarction within 12 months of starting study; unstable or poorly controlled angina pectoris) have been 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 **POMAXEL**, 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). Doctors 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 Syndrome (DRESS) have been reported with the use of pomalidomide (see section 4.8). 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 have been excluded from clinical studies. Such patients may be at higher risk of hypersensitivity reactions and should not receive **POMAXEL**. **POMAXEL** interruption or discontinuation should be considered for Grade 2-3 skin rash. **POMAXEL** must be discontinued for angioedema, anaphylactic reaction, 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

Dizziness and confusional state have been reported with the use of pomalidomide. 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. **POMAXEL** should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. **POMAXEL** 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 **POMAXEL** and as clinically indicated thereafter.

Infections

Reactivation of hepatitis B has been reported less frequently 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 **POMAXEL**. 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 **POMAXEL** 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. Doctors 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, **POMAXEL** must be permanently discontinued.

Sodium content

POMAXEL contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

Sugar content

POMAXEL contains sugar (isomalt), that may have a mild laxative effect.

Patients with rare hereditary problems of fructose intolerance should not take this medicine.

For information on other medicinal products given in combination with **POMAXEL**, refer to the respective current Professional Information.

4.5 Interactions with other medicines and other forms of interaction

Effect of **POMAXEL** on other medicines

POMAXEL is not anticipated to cause clinically relevant pharmacokinetic medicine-medicine interactions due to P450 isoenzyme inhibition or induction or transporter inhibition when co-administered with substrates of these enzymes or transporters. The potential for such medicine-medicine interactions, including the potential impact of **POMAXEL** on the pharmacokinetics of combined oral contraceptives, has not been evaluated clinically (see section 4.4 Teratogenicity).

Effect of other medicines on **POMAXEL**

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, has no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increases mean exposure to pomalidomide by 107 % with a 90 % confidence interval [91 % to 124 %] compared to pomalidomide plus ketoconazole. To evaluate the contribution of a CYP1A2 inhibitor alone to metabolism changes, co-administration of fluvoxamine alone with pomalidomide, increases 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 **POMAXEL**, patients

should be closely monitored for the occurrence of side effects, reduce the dose of **POMAXEL** by 50 %.

Dexamethasone

Co-administration of multiple doses of up to 4 mg **POMAXEL** with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of several CYP enzymes including CYP3A) to patients with multiple myeloma has no effect on the pharmacokinetics of **POMAXEL** compared with **POMAXEL** administered alone. Dexamethasone is a weak to moderate enzyme inducer.

The effect of dexamethasone on warfarin is unknown. Close monitoring of warfarin concentration is advised during treatment.

For information on other medicinal products given in combination with **POMAXEL**, refer to the respective current Professional Information.

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 **POMAXEL**, treatment must be stopped, and the patient should be referred to a doctor specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking **POMAXEL**, it is recommended to refer the female partner to a doctor specialised or experienced in teratology for evaluation and advice. Pomalidomide is present in human semen. As a precaution, all male patients taking **POMAXEL** 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

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

Breast-feeding

Breastfeeding of infants is contraindicated in mothers taking **POMAXEL**. It is unknown whether pomalidomide is excreted in human milk. Pomalidomide was detected in milk of lactating rats following administration to the mother.

Fertility

POMAXEL was found to impact negatively on fertility and be teratogenic in animals.

4.7 Effects on ability to drive and use machines

POMAXEL may cause fatigue, depressed level of consciousness, confusion, 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. If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks while being treated with **POMAXEL**.

4.8 Undesirable effects

a) Summary of the safety profile

POMAXEL in combination with bortezomib and dexamethasone

The most frequently reported blood and lymphatic system disorders were neutropenia, thrombocytopenia and anaemia. The most frequently reported adverse reaction was peripheral sensory neuropathy. The most frequently reported Grade 3 or 4 adverse events were blood and lymphatic system disorders including neutropenia, thrombocytopenia and anaemia. The most frequently reported serious adverse reaction was pneumonia. Other

serious adverse reactions reported included pyrexia, lower respiratory tract infection, pulmonary embolism, influenza and acute kidney injury.

POMAXEL in combination with dexamethasone

The most frequently reported adverse reactions are 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 and venous embolic or thrombotic (VTE) adverse reactions have been reported in patients. The most frequently reported Grade 3 or 4 adverse reactions are 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 is pneumonia. Other serious adverse reactions reported, include febrile neutropenia, neutropenia, thrombocytopenia and VTE adverse reactions.

Adverse reactions tend to occur more frequently within the first 2 cycles of treatment with **POMAXEL**.

b) Tabulated summary of adverse reactions

POMAXEL in combination with bortezomib and dexamethasone - Pomalidomide Adverse Drug Reactions (ADRs) in Relapsed and Refractory Multiple Myeloma Clinical Trial – After at least one prior therapy including lenalidomide:

The adverse drug reactions (ADRs) observed in patients treated with pomalidomide/bortezomib dexamethasone (PBd) are listed below by system organ class and frequency for all ADRs and grade 3/4 ADRs. The ADRs in this section have been assessed

as being at least possibly related to pomalidomide when used in combination with low-dose dexamethasone.

	All ADRs		**Grade 3/4 ADRs**	
System organ class	PBd	Bd	PBd	Bd
Infections and infestations				
Upper respiratory tract infection	Frequent	Frequent	Frequent	Frequent
Pneumonia	Frequent	Frequent	Frequent	Frequent
Bronchitis	Frequent	Frequent	Frequent	Frequent
Viral upper respiratory tract infection	Frequent	Frequent	-	-
Influenza	Frequent	Frequent	Frequent	Frequent
Urinary tract infection	Frequent	Frequent	Frequent	Less frequent
Respiratory tract infection	Frequent	Frequent	Frequent	-
Lower respiratory tract infection	Frequent	Frequent	Frequent	Less frequent
Sepsis	Frequent	Less frequent	Frequent	Less frequent
Septic shock	Frequent	-	Frequent	-
Clostridium difficile colitis	Frequent	Less frequent	Frequent	-
Lung infection	Frequent	Frequent	Frequent	-
Bronchiolitis	Frequent	-	Frequent	-
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Basal cell carcinoma	Frequent	Less frequent	-	Less frequent
Blood and lymphatic system disorders				
Neutropenia	Frequent	Frequent	Frequent	Frequent
Thrombocytopenia	Frequent	Frequent	Frequent	Frequent
Anaemia	Frequent	Frequent	Frequent	Frequent
Leukopenia	Frequent	Frequent	Frequent	Frequent

Lymphopenia	Frequent	Frequent	Frequent	Frequent
Febrile neutropenia	Frequent	-	Frequent	-
Metabolism and nutrition disorders				
Hypokalaemia	Frequent	Frequent	Frequent	Frequent
Hyperglycaemia	Frequent	Frequent	Frequent	Frequent
Hypomagnesemia	Frequent	Frequent	Frequent	Less frequent
Hypocalcaemia	Frequent	Frequent	Frequent	Less frequent
Hypophosphatemia	Frequent	Frequent	Frequent	Frequent
Hyperkalaemia	Frequent	Frequent	Frequent	Less frequent
Hypercalcaemia	Frequent	Frequent	Frequent	Less frequent
Psychiatric disorders				
Insomnia	Frequent	Frequent	Frequent	Less frequent
Depression	Frequent	Frequent	Frequent	-
Nervous system disorders				
Peripheral sensory neuropathy	Frequent	Frequent	Frequent	Frequent
Dizziness	Frequent	Frequent	Less frequent	Less frequent
Tremor	Frequent	Frequent	Less frequent	-
Dysgeusia	Frequent	Frequent	-	-
Syncope	Frequent	Frequent	Frequent	Frequent
Peripheral sensorimotor neuropathy	Frequent	Frequent	Frequent	Less frequent
Paraesthesia	Frequent	Frequent	-	-
Eye disorders				
Cataract	Frequent	-	Frequent	-
Cardiac disorders				
Atrial fibrillation	Frequent	Frequent	Frequent	Less frequent
Vascular disorders				

Hypotension	Frequent	Frequent	Frequent	Less frequent
Hypertension	Frequent	Frequent	Frequent	Frequent
Deep vein thrombosis	Frequent	Frequent	Less frequent	Less frequent
Respiratory, thoracic and mediastinal disorders				
Cough	Frequent	Frequent	-	-
Dyspnoea	Frequent	Frequent	Frequent	Frequent
Pulmonary embolism	Frequent	Frequent	Frequent	Less frequent
Gastrointestinal disorders				
Constipation	Frequent	Frequent	Frequent	Less frequent
Diarrhoea	Frequent	Frequent	Frequent	Frequent
Nausea	Frequent	Frequent	Less frequent	Less frequent
Vomiting	Frequent	Frequent	Frequent	Less frequent
Abdominal pain	Frequent	Frequent	Frequent	Frequent
Abdominal pain upper	Frequent	Frequent	Less frequent	-
Stomatitis	Frequent	Frequent	Less frequent	-
Dry mouth	Frequent	Frequent	-	-
Abdominal distension	Frequent	Frequent	Less frequent	-
Skin and subcutaneous tissue disorders				
Rash	Frequent	Frequent	Frequent	-
Musculoskeletal and connective tissue disorders				
Back pain	Frequent	Frequent	Frequent	Frequent
Muscular weakness	Frequent	Frequent	Frequent	Less frequent
Muscle spasms	Frequent	Frequent	-	-
Bone pain	Frequent	Frequent	Less	Frequent

			frequent	
Renal and urinary disorders				
Acute kidney injury	Frequent	Frequent	Frequent	Frequent
Chronic kidney disease	Frequent	-	Frequent	-
Urinary retention	Frequent	-	Frequent	-
General disorders and administration site conditions				
Fatigue	Frequent	Frequent	Frequent	Frequent
Oedema, peripheral	Frequent	Frequent	Frequent	Less frequent
Pyrexia	Frequent	Frequent	Frequent	Less frequent
Non-cardiac chest pain	Frequent	Frequent	Frequent	Less frequent
Oedema	Frequent	Less frequent	Frequent	-
Investigations				
Weight decreased	Frequent	Frequent	Frequent	-
Alanine aminotransferase increased	Frequent	Frequent	Less frequent	Less frequent
Injury, poisoning and procedural complications				
Fall	Frequent	Frequent	Less frequent	-

POMAXEL in combination with dexamethasone - Pomalidomide Adverse Drug Reactions (ADRs) in Relapsed and Refractory Multiple Myeloma Clinical Trial – After at least two prior therapies including lenalidomide and a proteasome inhibitor:

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

The following adverse reactions (ADRs) to be considered in patients treated with POMAXEL, in combination with dexamethasone:

System organ class	All ADRs/Frequency	Grade

		3−4 ADRs/Frequency
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	**Frequent** Neutropenic sepsis Pneumonia (bacterial, viral and fungal infections, including opportunistic infections) Bronchopneumonia Respiratory tract infection Upper respiratory 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 Leukopenia Anaemia Febrile neutropenia Pancytopenia	**Frequent** Neutropenia Thrombocytopenia Leukopenia Anaemia Febrile neutropenia Pancytopenia
Immune system disorders	**Frequent** Angioedema Urticaria **Frequency unknown** Anaphylactic reaction	**Less frequent** Angioedema Urticaria **Frequency unknown** Anaphylactic reaction
Endocrine disorders	**Less frequent** Hypothyroidism	
Metabolism and nutrition disorders	**Frequent** Decreased appetite Hyperkalaemia Hyponatraemia Hyperuricaemia **Less frequent** Tumour lysis syndrome	**Frequent** Hyperkalaemia Hyponatraemia Hyperuricaemia **Less frequent** Decreased appetite Tumour lysis syndrome
Psychiatric disorders	**Frequent** Confusional state	**Frequent** Confusional state
Nervous system disorders	**Frequent**	**Frequent**

	Depressed level of consciousness Peripheral sensory neuropathy Dizziness Tremor Intracranial haemorrhage **Less frequent** Cerebrovascular accident	Depressed level of consciousness **Less frequent** Peripheral sensory neuropathy Dizziness Tremor Cerebrovascular accident Intracranial haemorrhage
Ear and labyrinth disorders	**Frequent** Vertigo	**Frequent** Vertigo
Cardiac disorders	**Frequent** Cardiac failure Atrial fibrillation Myocardial infarction	**Frequent** Atrial fibrillation Cardiac failure **Less frequent** Myocardial infarction
Vascular disorders	**Frequent** Deep vein thrombosis	**Less frequent** Deep vein thrombosis
Respiratory system, thoracic and mediastinal disorders	**Frequent** Dyspnoea Cough Pulmonary embolism Epistaxis Interstitial lung disease	**Frequent** Dyspnoea **Less frequent** Cough Pulmonary embolism Epistaxis Interstitial lung disease
Gastrointestinal disorders	**Frequent** Diarrhoea Nausea Constipation Vomiting Gastrointestinal haemorrhage	**Frequent** Diarrhoea Vomiting Constipation **Less frequent** Nausea Gastrointestinal haemorrhage
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	**Frequent** Bone pain **Less frequent** Muscle spasms
Renal and urinary disorders	**Frequent** Renal failure Urinary retention	**Frequent** Renal failure **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	**Frequent** Fatigue Pyrexia Oedema peripheral
Investigations	**Frequent** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased Blood uric acid increased	**Frequent** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased **Less frequent** Blood uric acid increased

Pomalidomide Adverse Drug Reactions (ADRs) in Paediatric Patients with Recurrent or Progressive Brain Tumours

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

Post-marketing data:

The following adverse reactions have been identified from the worldwide post-marketing experience with pomalidomide.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to pomalidomide exposure.

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 (including 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).

c) Description of selected adverse reactions

Teratogenicity

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

Neutropenia and thrombocytopenia

Neutropenia occurs in patients who receive pomalidomide plus low dose dexamethasone (Pom + LD-Dex), as well as in patients who receive high dose dexamethasone (HD-Dex). Neutropenia (Grade 3 or 4) occurs more often in patients who received Pom + LD-Dex, compared with patients who receive Pom + HD-Dex.

In Pom + LD-Dex treated patients, neutropenia is infrequently serious, does not lead to treatment discontinuation, and is associated with treatment interruption and with dose reduction in patients.

Febrile neutropenia (FN) has been reported and may be serious (see section 4.2 and 4.4). Febrile neutropenia (FN) is experienced in patients who receive Pom + LD-Dex, and in no patients who receive Pom + HD-Dex. All are reported to be Grade 3 or 4. FN is reported to be infrequently serious in patients. FN is associated with dose interruption and with dose reduction in patients, and with no treatment discontinuations.

Thrombocytopenia occurs in patients who receive Pom + LD-Dex, and in patients who receive Pom + HD-Dex. Thrombocytopenia (Grade 3 or 4) occurs equally in patients who receive Pom + LD-Dex compared to patient receiving Pom + HD-Dex. In Pom + LD-Dex treated patients, thrombocytopenia is infrequently serious in patients, that leads to dose reduction, dose interruption and treatment discontinuation in patients (see section 4.4 and section 4.6).
In patients receiving combination therapy with pomalidomide, thrombocytopenia may occur. Thrombocytopenia (Grade 3 or 4) can lead to **POMAXEL** discontinuation and may be serious (see sections 4.2 and 4.4).

Neutropenia and thrombocytopenia tend to occur more frequently within the first 2 cycles of treatment with **POMAXEL**.

Infection

Infection is the most frequent non haematological toxicity.

Infection do occur in patients who receive Pom + LD-Dex, and in patients who receive HD-Dex. Approximately half of those infections are Grade 3 or 4; in Pom + LD-Dex-treated and in patients who receive HD-Dex.

In Pom + LD-Dex treated patients, pneumonia and upper respiratory tract infections are the most frequently reported infections; with some reported infections being serious and fatal infections (Grade 5) occurring in treated patients. In Pom + LD-Dex treated patients, infections lead to dose discontinuation, treatment interruption and dose reduction in patients.

Thromboembolic events

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).

In patients receiving combination therapy with pomalidomide, venous thromboembolic events (VTE) may occur. VTE may be serious, no fatal reactions have been reported, and VTE was not associated with **POMAXEL** discontinuation.

Peripheral neuropathy

- ***POMAXEL*** *in combination with dexamethasone*

Patients with ongoing peripheral neuropathy ≥ Grade 2 are excluded from studies.

Peripheral neuropathy, mostly Grade 1 or 2 occurs equally in patients who receive Pom + LD-Dex, compared to patients who receive Pom + HD-Dex. Grade 3 or 4 reactions occurs equally in patients who receive Pom + LD-Dex compared to patients who receive Pom + HD-Dex. In patients treated with Pom + LD-Dex, no peripheral neuropathy reactions are reported to have been serious in studies and peripheral neuropathy leads to dose discontinuation in patients (see section 4.4 and section 4.6).

Peripheral neuropathy may occur. No peripheral neuropathy reactions have been reported as serious, and peripheral neuropathy may lead to dose discontinuation (see section 4.4).

Haemorrhage

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

Allergic reactions and severe skin reactions

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

Paediatric population

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

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. Healthcare 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 side effects (see section 4.8). Treatment should be symptomatic. It is unknown whether pomalidomide or its metabolites are dialysable.

In the event of overdose, supportive care is advised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A32 Other – Immunomodulators

Pharmacotherapeutic group: Immunosuppressants, 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), cullins-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 are manifested as a delayed erythroid maturation, increased proliferation of immature erythroid cells, and induction of foetal haemoglobin (HbF) production.

A QTc study was conducted to evaluate the effects of pomalidomide on QT interval at single doses of 4 mg and 20 mg. A single dose of pomalidomide up to 20 mg was not associated with prolongation of the QT interval in healthy male subjects. Pomalidomide is not expected to result in clinically significant prolongation of the QT interval in patients at the approved therapeutic doses.

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

5.2 Pharmacokinetic properties

Absorption

Pomalidomide is absorbed with a 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 approximately 27 %, 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.

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 are 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, has no clinically relevant effect on exposure to pomalidomide.

Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increases exposure to pomalidomide by 107 % with a 90 % confidence interval [91 % to 124 %] compared to pomalidomide plus ketoconazole. In a second study to evaluate 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 157 %] compared to pomalidomide alone.

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

Administration of pomalidomide in smokers, with smoking tobacco known to induce the CYP1A2 isoform, had no clinically relevant effect on exposure to pomalidomide compared to that exposure to pomalidomide observed in non-smokers.

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 has no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.

Pomalidomide is a substrate of P-glycoprotein *in vitro*, but this does not appear to limit its absorption in humans, where at least 73 % of the substance is absorbed. Co-administration of pomalidomide with the P-gp inhibitor ketoconazole has no clinically relevant effect on exposure to pomalidomide, therefore based on this, clinically relevant medicine-medicine 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 medicine-medicine 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 is 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 account for 10 % (2 % in urine and 8 % in faeces).

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

Pharmacokinetics in Children

Following a single oral dose of pomalidomide in children and young adults with recurrent or progressive primary brain tumour, the median T_{max} was 2 to 4 hours post dose and

corresponded to geometric mean C_{max} (CV %) values of 74,8 (59,4 %), 79,2 (51,7 %), and 104 (18,3 %) ng/mL at the 1,9, 2,6, and 3,4 mg/m^2 dose levels, respectively. AUC_{0-24} and AUC_{0-inf} followed similar trends, with total exposure in the range of approximately 700 to 800 h·ng/mL at the lower 2 doses, and approximately 1200 h·ng/mL at the high dose. Estimates of $t_{½}$ were in the range of approximately 5 to 7 hours. There were no clear trends attributable to stratification by age and steroid use at the MTD.

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

The pharmacokinetics of pomalidomide following oral administration at dose levels of 1,9 mg/m^2/day to 3,4 mg/m^2/day were determined in 70 patients with ages from 4 to 20 years in an integrated analysis of a Phase 1 and Phase 2 study in recurrent or progressive paediatric brain tumours. Pomalidomide concentration-time profiles were adequately described with a one compartment PK model with first-order absorption and elimination. Pomalidomide exhibited linear and time-invariant PK with moderate variability. The typical values of CL/F, Vc/F, Ka, lag time of pomalidomide were 3,94 L/h, 43,0 L, 1,45 h-1 and 0,454 h respectively. The terminal elimination half-life of pomalidomide was 7,33 hours. Except for BSA, none of the tested covariates including age and sex had effect on pomalidomide PK. Although BSA was identified as a statistically significant covariate of pomalidomide CL/F and Vc/F, the impact of BSA on exposure parameters was not deemed clinically relevant.

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

Pharmacokinetics in the Elderly

In subjects, aged 61 to 82, the mean pharmacokinetic parameters of $AUC_{(0-\infty)}$ and C_{max} were generally similar to younger subjects.

Pharmacokinetics in 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 m^2) 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 m^2) 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.

Pharmacokinetics in 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

Capsule contents:

Isomalt, pregelatinized starch, sodium stearyl fumarate.

Capsule shell:

POMAXEL *1 mg capsules*

Gelatin, yellow iron oxide, titanium dioxide

POMAXEL *2 mg capsules*

Gelatin, titanium dioxide, red iron oxide, yellow iron oxide

POMAXEL *3 mg capsules*

Gelatin, titanium dioxide, Brilliant blue FCF-FD&C Blue 1

POMAXEL *4 mg capsules*

Gelatin, titanium dioxide, FD&C Red #3, Brilliant blue FCF-FD&C Blue 1

Printing ink on all capsules:

Shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, black iron oxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C. Keep in the outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

POMAXEL is packed in PVC/Aclar-Aluminum blisters and Aluminum-Aluminum blisters. Pack size: 21 capsules (7 capsules x 3 blisters) per box and 40 capsules (8 capsules x 5 blisters) per box.

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 providers 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 returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBERS

POMAXEL 1 mg: 56/32/0721

POMAXEL 2 mg: 56/32/0722

POMAXEL 3 mg: 56/32/0723

POMAXEL 4 mg: 56/32/0724

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 July 2023

10 DATE OF REVISION OF TEXT

24 April 2024