1.3.1.1. Professional Information for medicines for human use

SCHEDULING STATUS:

S4

1 NAME OF THE MEDICINE

IMNOVID® 1 mg (hard capsules)

IMNOVID® 2 mg (hard capsules)

IMNOVID® 3 mg (hard capsules)

IMNOVID® 4 mg (hard capsules)

2 QUALITIVE AND QUANTITIVE COMPOSITION

Each IMNOVID 1 mg hard capsule contains 1,0 mg of pomalidomide.

Each IMNOVID 2 mg hard capsule contains 2,0 mg of pomalidomide.

Each IMNOVID 3 mg hard capsule contains 3,0 mg of pomalidomide.

Each IMNOVID 4 mg hard capsule contains 4,0 mg of pomalidomide.

Contains sugar: Mannitol

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

IMNOVID 1 mg: Dark blue opaque cap on yellow opaque body, imprinted with black ink on body and white ink on cap, size 3, hard gelatin capsules.

IMNOVID 2 mg: Dark blue opaque cap on orange opaque body, imprinted with white ink on cap and body, size 1, hard gelatin capsules.

IMNOVID 3 mg: Dark blue opaque cap on green opaque body, imprinted with white ink on cap and body, size 1, hard gelatin capsules.

IMNOVID 4 mg: Dark blue opaque cap on blue opaque body, imprinted with white ink on cap and body, size 1, hard gelatin capsules.

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 Fertility, pregnancy and lactation).

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 IMNOVID AS NEGLIGIBLE AS POSSIBLE, IMNOVID IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME. THIS PROGRAMME IS CALLED THE KEY ASSIST RISK MANAGEMENT PROGRAMME.

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

WARNING: VENOUS THROMBO EMBOLISM:

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

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

IMNOVID 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.

IMNOVID in combination with dexamethasone (Pd) is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and a proteasome inhibitor (e.g. bortezomib), and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

Posology

Treatment must be initiated and monitored under the supervision of 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 IMNOVID 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.

IMNOVID dose modification or interruption

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

Dose modification instructions for IMNOVID for haematologic toxicities:

Toxicity	**Dose Modification**
Neutropenia	
• ANC < 500/µL or Febrile neutropenia (fever ≥ 38,5°C and ANC <1 000/µL)	Interrupt IMNOVID treatment, follow CBC weekly. Add G-CSF (at the discretion of the treating doctor)
• Pd regimen: ANC return to ≥500/µL • PBd regimen: ANC return to ≥1000/µL	Resume pomalidomide at 3 mg daily.

• For each subsequent drop < 500/µL • Pd regimen: Return to ≥ 500/µL • PBd regimen: Return to ≥ 1000/µL	Interrupt IMNOVID treatment Resume IMNOVID at 1 mg less than the previous dose
Thrombocytopenia • Platelets < 25 000/µL • Platelets return to > 50 000/µL	Interrupt IMNOVID treatment, follow CBC weekly Resume IMNOVID treatment at 3 mg daily
• For each subsequent drop < 25 000/µL • Return to ≥ 50000/µL	Interrupt IMNOVID treatment Resume IMNOVID at 1 mg less than previous dose.

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

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

Pd regimen: To initiate a new cycle of IMNOVID, 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 IMNOVID, 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 IMNOVID, reduce the recommended starting IMNOVID 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 Dyspepsia ≥ Grade 3	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist. 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 3dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤ Grade 2. Resume with dose reduced by one level.

Discontinuation of IMNOVID

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

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

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

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

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

Special populations

Elderly population

No dose adjustment is required for IMNOVID.

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 IMNOVID is required for patients with renal impairment. On haemodialysis days, patients should take their IMNOVID 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 IMNOVID 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.

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

4.3 Contraindications

- Hypersensitivity to IMNOVID (pomalidomide) or to any of the excipients.
- Pregnancy and lactation (see section 4.6 Fertility, pregnancy and lactation)
- Females of childbearing potential, unless all the conditions of the pregnancy prevention programme are met (see section 4.4 Special warnings and precautions for use)
- Male patients unable to follow or comply with the required contraceptive measures (see section 4.4 Special warnings and precautions for use)

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

The conditions of the Key Assist Risk Management Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Criteria for females of non-childbearing potential

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

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 2 ~~1~~ years*.
- Premature ovarian failure confirmed by a specialist gynaecologist.
- Previous bilateral salpingo-oophorectomy, or hysterectomy.
- XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential.

Counselling

For females of childbearing potential, IMNOVID is contraindicated unless all of the following are met:

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

The prescriber must ensure that for females of childbearing potential:

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

For male patients taking IMNOVID, pharmacokinetic data has demonstrated that pomalidomide is present in human semen. As a precaution, all male patients taking IMNOVID 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 IMNOVID or for 4 weeks after he has stopped taking IMNOVID, 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 IMNOVID therapy unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained health care professional for contraceptive advice in order that contraception can be initiated.

The following can be considered to be examples of suitable methods of contraception:

Highly effective methods

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

Effective methods

- Male condom.
- Diaphragm.
- Cervical cap.

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

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of ~~50~~ 25 mIU/ml must be performed for females of childbearing potential as outlined below. This requirement includes females of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of IMNOVID 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 IMNOVID 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 IMNOVID.

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 IMNOVID, 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 IMNOVID.

Additional precautions

Patients should be instructed never to give IMNOVID 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 IMNOVID.

Educational materials

In order to assist patients in avoiding foetal exposure to pomalidomide, Key Oncologics will provide educational material to healthcare professionals to reinforce the warnings about the expected teratogenicity of IMNOVID, 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 Key Assist Risk Management Programme should be given by the medical practitioner to females of childbearing potential and, as appropriate, to male patients.

Haematological events

Neutropenia was the most frequently reported Grade 3/4 haematologic adverse reaction (AR) in subjects with relapsed/refractory multiple myeloma, followed by anaemia and thrombocytopenia. Monitor patients for haematologic toxicities, especially neutropenia.

Patients should be advised to report febrile episodes promptly. Medical practitioners should observe patients for signs of bleeding including epistaxes, especially with use of concomitant medicines known to increase the risk of bleeding (see Section 4.8).

Monitor complete blood counts at baseline, weekly for the first 8 weeks and monthly thereafter. A dose modification may be required. Patients may require use of blood product support and/or growth factors.

Thromboembolic events

Patients receiving IMNOVID have commonly developed venous thromboembolic events (VTE) (predominantly deep vein thrombosis and pulmonary embolism) and arterial thrombotic events (myocardial infarction and cerebrovascular accident). Patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Patients and medical practitioners are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, arm or leg swelling. Anti- coagulation therapy (unless contraindicated) is

recommended, (such as acetylsalicylic acid, warfarin, heparin or clopidogrel), especially in patients with additional thrombotic risk factors. A decision to take prophylactic measures should be made after a careful assessment of the individual patient's underlying risk factors. In clinical studies, patients received prophylactic acetylsalicylic acid or alternative anti- thrombotic therapy. The use of erythropoietic agents carries a risk of thrombotic events including thromboembolism. Therefore, erythropoietic agents, a 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 III 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

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

Allergic reactions and Serious Skin Reactions

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

Dizziness and confusion

Confusion, fatigue, depressed level of consciousness and dizziness have been reported with the use of IMNOVID. 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. IMNOVID should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be should only be resumed after a thorough evaluation of the benefits and the risks.

Hepatic Disorders

Markedly elevated levels of alanine aminotransferase and bilirubin have been observed in patients treated with IMNOVID (see section 4.8). There have also been cases of hepatitis that resulted in discontinuation of IMNOVID. Regular monitoring of liver function is recommended.

Infection

Reactivation of hepatitis B has been reported rarely in patients receiving IMNOVID 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 IMNOVID. Caution should be exercised when IMNOVID in combination with dexamethasone is used in patients previously infected with HBV. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Sodium content

IMNOVID contains less than 1 mmol sodium (23 mg) per capsule, i.e. essentially ‘sodium-free’.

IMNOVID contains mannitol and may have a laxative effect.

Patients with the rare hereditary condition of mannitol intolerance should not take IMNOVID.

4.5 Interaction with other medicines and other forms of Interaction

Effect of IMNOVID on other medicines

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

Effect of other medicines on IMNOVID

Pomalidomide is partly metabolised by CYP1A2 and CYP3A4/5. It is also a substrate for P-glycoprotein. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased exposure to pomalidomide by 104 % with a 90 % confidence interval [88 % to 122 %] compared to pomalidomide plus ketoconazole. 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 156 %] compared to pomalidomide alone.

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

Dexamethasone

Co-administration of multiple doses of 4 mg IMNOVID 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 IMNOVID, 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 IMNOVID, 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 IMNOVID should use condoms throughout treatment duration, during dose interruption and for 4 weeks after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception (see section 4.4 Special warnings and precautions for use)

Pregnancy

IMNOVID is contraindicated during pregnancy and in women of childbearing potential (see section 4.3 Contraindications)

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

4.7 Effects on ability to drive and use machines

IMNOVID 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

PBd Treatment Regimen - Pomalidomide Adverse Drug Reactions (ADRs) in Relapsed and Refractory Multiple Myeloma Clinical Trial (MM-007) – 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, grade 3/4 ADRs and serious 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 and bortezomib and are presented in accordance with the CIOMS Working Groups III and V guidance document, with frequency categories defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); and uncommon (≥ 1/1 000 to < 1/100). Considerations for determining an ADR included: biological/pharmacological plausibility for a drug-event relationship, known morbidities of target population and disease being treated, adverse reactions suspected with drugs of this class, and weight of evidence (e.g., positive rechallenge, positive dechallenge, time to onset, lack of confounding factors). Additionally, medical judgment was applied to determine exceptions for inclusion and exclusion, as necessary.

Table 3: PBd Treatment Regimen: Adverse Drug Reactions (ADRs) in Relapsed or Refractory Multiple Myeloma in patients who have received at least one prior treatment regimen including lenalidomide (MM007: Safety Population)

	All ADRs[1]		**Grade 3/4 ADRs[2]**		**Serious ADRs[3]**	
System Organ Class Preferred Term	PBd (N=278) n (%) Frequency	Bd (N=270) n (%) Frequency	PBd (N=278) n (%) Frequency	Bd (N=270) n (%) Frequency	PBd (N=278) n (%)	Bd (N=270) n (%)
Infections and infestations						

Upper respiratory tract infection	58 (20,9) *Very common*	48 (17,8) *Very common*	3 (1,1) *Common*	3 (1,1) *Common*	2 (0,7)	3 (1,1)
Pneumonia	53 (19,1) *Very common*	37 (13,7) *Very common*	32 (11,5) *Very common*	17 (6,3) *Common*	32 (11,5)	17 (6,3)
Bronchitis	39 (14,0) *Very common*	19 (7,0) *Common*	4 (1,4) *Common*	3 (1,1) *Common*	3 (1,1)	2 (0,7)
Viral upper respiratory tract infection	31 (11,2) *Very common*	14 (5,2) *Common*	0	0	0	0
Influenza	27 (9,7) *Common*	15 (5,6) *Common*	7 (2,5) *Common*	4 (1,5) *Common*	8 (2,9)	4 (1,5)
Urinary tract infection	27 (9,7) *Common*	25 (9,3) *Common*	4 (1,4) *Common*	1 (0,4) *Uncommon*	2 (0,7)	0
Respiratory tract infection	23 (8,3) *Common*	12 (4,4) *Common*	4 (1,4) *Common*	0	6 (2,2)	0
Lower respiratory tract infection	22 (7,9) *Common*	7 (2,6) *Common*	4 (1,4) *Common*	2 (0,7) *Uncommon*	8 (2,9)	2 (0,7)
Sepsis	6 (2,2) *Common*	1 (0,4) *Uncommon*	6 (2,2) *Common*	1 (0,4) *Uncommon*	5 (1,8)	1 (0,4)
Septic shock	6 (2,2) *Common*	0	4 (1,4) *Common*	0	6 (2,2)	0
Clostridium difficile colitis	4 (1,4) *Common*	1 (0,4) *Uncommon*	3 (1,1) *Common*	0	4 (1,4)	0

Lung infection	4 (1,4) *Common*	3 (1,1) *Common*	3 (1,1) *Common*	0	3 (1,1)	1 (0,4)
Bronchiolitis	4 (1,4) *Common*	0	3 (1,1) *Common*	0	1 (0,4)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Basal cell carcinoma	4 (1,4) *Common*	1 (0,4) *Uncommon*	0	1 (0,4) *Uncommon*	4 (1,4)	1 (0,4)
Blood and lymphatic system disorders						
Neutropenia	130 (46,8) *Very common*	29 (10,.7) *Very common*	116 (41,7) *Very common*	23 (8,5) *Common*	1 (0,4)	0
Thrombocytopenia[4]	102 (36,7) *Very common*	103 (38,1) *Very common*	76 (27,3) *Very common*	79 (29,3) *Very common*	1 (0,4)	3 (1,1)
Anemia[4]	79 (28,4) *Very common*	73 (27,0) *Very common*	39 (14,0) *Very common*	38 (14,1) *Very common*	3 (1,1)	5 (1,9)
Leukopenia	32 (11,5) *Very common*	9 (3,3) *Common*	15 (5,4) *Common*	5 (1,9) *Common*	0	0
Lymphopenia	12 (4,3) *Common*	9 (3,3) *Common*	12 (4.,3) *Common*	8 (3,0) *Common*	1 (0,4)	0
Febrile neutropenia	9 (3,2) *Common*	0	9 (3,2) *Common*	0	5 (1,8)	0
Metabolism and nutrition disorders						

Hypokalemia	43 (15,5) *Very common*	30 (11,1) *Very common*	17 (6,1) *Common*	11 (4,1) *Common*	0	0
Hyperglycemia	40 (14,4) *Very common*	30 (11,1) *Very common*	25 (9,0) *Common*	14 (5,2) *Common*	3 (1,1)	1 (0,4)
Hypomagnesemia	19 (6,8) *Common*	7 (2,6) *Common*	5 (1,8) *Common*	2 (0,7) *Uncommon*	0	1 (0,4)
Hypocalcemia	18 (6,5) *Common*	9 (3,3) *Common*	5 (1,8) *Common*	1 (0,4) *Uncommon*	0	0
Hypophosphatemia	16 (5,8) *Common*	8 (3,0) *Common*	11 (4,0) *Common*	5 (1,9) *Common*	0	0
Hyperkalemia	11 (4,0) *Common*	6 (2,2) *Common*	7 (2,5) *Common*	2 (0,7) *Uncommon*	0	0
Hypercalcemia	11 (4,0) *Common*	4 (1,5) *Common*	4 (1,4) *Common*	1 (0,4) *Uncommon*	1 (0,4)	0
Psychiatric disorders						
Insomnia	45 (16,2) *Very common*	53 (19,6) *Very common*	5 (1,8) *Common*	2 (0,7) *Uncommon*	0	0
Depression	15 (5,4) *Common*	7 (2,6) *Common*	3 (1,1) *Common*	0	1 (0,4)	0
Nervous system disorders						
Peripheral sensory neuropathy	133 (47,8) *Very common*	100 (37,0) *Very common*	23 (8,3) *Common*	12 (4,4) *Common*	0	1 (0,4)

Dizziness	48 (17,3) *Very common*	28 (10,4) *Very common*	1 (0,4) *Uncommon*	1 (0,4) *Uncommon*	0	1 (0,4)
Tremor	30 (10,8) *Very common*	8 (3,0) *Common*	1 (0,4) *Uncommon*	0	0	0
Dysgeusia	18 (6,5) *Common*	8 (3,0) *Common*	0	0	0	0
Syncope	17 (6,1) *Common*	11 (4,1) *Common*	14 (5,0) *Common*	6 (2,2) *Common*	6 (2,2)	5 (1,9)
Peripheral sensorimotor neuropathy	16 (5,8) Common	12 (4,4) *Common*	5 (1,8) *Common*	1 (0,4) *Uncommon*	0	0
Paresthesia	16 (5,8) *Common*	5 (1,9) *Common*	0	0	0	0
Eye disorders						
Cataract	10 (3,6) *Common*	0	3 (1,1) *Common*	0	0	0
Cardiac disorders						
Atrial fibrillation	26 (9,4) *Common*	5 (1,9) *Common*	9 (3,2) *Common*	2 (0,7) *Uncommon*	7 (2,5)	2 (0,7)
Vascular disorders						
Hypotension	24 (8,6) *Common*	14 (5,2) *Common*	5 (1,8) *Common*	1 (0,4) *Uncommon*	3 (1,1)	1 (0,4)
Hypertension	18 (6,5) *Common*	17 (6,3) *Common*	8 (2,9) *Common*	4 (1,5) *Common*	0	0

Deep vein thrombosis	14 (5,0) *Common*	5 (1,9) *Common*	2 (0,7) *Uncommon*	1 (0,4) *Uncommon*	4 (1,4)	4 (1,5)
Respiratory, thoracic and mediastinal disorders						
Cough	57 (20,5) *Very common*	40 (14,8) *Very common*	0	0	0	0
Dyspnea	56 (20,) *Very common*	33 (12,2) *Very common*	8 (2,9) *Common*	3 (1,1) *Common*	4 (1,4)	1 (0,4)
Pulmonary embolism	11 (4,0) *Common*	1 (0,4) *Common*	11 (4,0) *Common*	1 (0,4) *Uncommon*	8 (2,9)	1 (0,4)
Gastrointestinal disorders						
Constipation	102 (36,7) *Very common*	65 (24,1) *Very common*	7 (2,5) *Common*	1 (0,4) *Uncommon*	2 (0,7)	2 (0,7)
Diarrhea	94 (33,8) *Very common*	81 (30,0) *Very common*	20 (7,2) *Common*	9 (3,3) *Common*	5 (1,8)	6 (2,2)
Nausea[4]	49 (17,6) *Very common*	54 (20,0) *Very common*	1 (0,4) *Uncommon*	1 (0,4) *Uncommon*	1 (0,4)	2 (0,7)
Vomiting[4]	32 (11,5) *Very common*	27 (10,0) *Very common*	3 (1,1) *Common*	1 (0,4) *Uncommon*	1 (0,4)	2 (0,7)
Abdominal pain	27 (9,7) *Common*	18 (6,7) *Common*	4 (1,4) *Common*	4 (1,5) *Common*	2 (0,7)	1 (0,4)

Abdominal pain upper	22 (7,9) *Common*	15 (5,6) *Common*	1 (0,4) *Uncommon*	0	2 (0,7)	0
Stomatitis	17 (6,1) *Common*	1 (0,4) *Common*	1 (0,4) *Uncommon*	0	0	0
Dry mouth	16 (5,8) *Common*	10 (3,7) *Common*	0	0	0	0
Abdominal distension	15 (5,4) *Common*	6 (2,2) *Common*	1 (0,.) *Uncommon*	0	0	0
Skin and subcutaneous tissue disorders						
Rash	26 (9,4) *Common*	8 (3,0) *Common*	6 (2,2) *Common*	0	1 (0,4)	0
Musculoskeletal and connective tissue disorders						
Back pain	52 (18,7) *Very common*	36 (13,3) *Very common*	3 (1,1) *Common*	4 (1,5) *Common*	3 (1,1)	1 (0,4)
Muscular weakness	38 (13,7) *Very common*	13 (4,8) *Common*	3 (1,1) *Common*	1 (0,4) *Uncommon*	1 (0,4)	1 (0,4)
Muscle spasms	26 (9,4) *Common*	14 (5,2) *Common*	0	0	0	0
Bone pain	22 (7,9) *Common*	15 (5,6) *Common*	1 (0,4) *Uncommon*	3 (1,1) *Common*	1 (0,4)	1 (0,4)
Renal and urinary disorders						
Acute kidney injury	15 (5,4) *Common*	10 (3,7) *Common*	9 (3,2) *Common*	4 (1,5) *Common*	8 (2,9)	6 (2,2)
Chronic kidney disease	6 (2,2) *Common*	0	3 (1,1) *Common*	0	1 (0,4)	0

Urinary retention	4 (1,4) *Common*	0	3 (1,1) *Common*	0	1 (0,4)	0
General disorders and administration site conditions						
Fatigue	103 (37,1) *Very common*	71 (26,3) *Very common*	23 (8,3) *Common*	10 (3,7) *Common*	1 (0,4)	0
Edema, peripheral	94 (33,8) *Very common*	54 (20,0) *Very common*	5 (1,8) *Common*	2 (0,7) *Uncommon*	0	0
Pyrexia	64 (23,0) *Very common*	32 (11,9) *Very common*	6 (2,2) *Common*	2 (0,7) *Uncommon*	11 (4,0)	5 (1,9)
Non-cardiac chest pain	14 (5,0) *Common*	13 (4,8) *Common*	4 (1,4) *Common*	1 (0,4) *Uncommon*	3 (1,1)	2 (0,7)
Edema	10 (3,6) *Common*	1 (0,4) *Uncommon*	4 (1,4) *Common*	0	0	0
Investigations						
Weight decreased	16 (5,8) *Common*	17 (6,3) *Common*	3 (1.1) *Common*	0	0	0
Alanine aminotransferase increased[4]	13 (4,7) *Common*	3 (1,1) *Common*	2 (0,7) *Uncommon*	1 (0,.4) *Uncommon*	0	0
Injury, poisoning and procedural complications						
Fall	17 (6,1) *Common*	10 (3,7) *Common*	1 (0,.4) *Uncommon*	0	0	0

Pd Treatment Regimen - Pomalidomide Adverse Drug Reactions (ADRs) in Relapsed and Refractory Multiple Myeloma Clinical Trial (MM-003) – After at least two prior therapies including lenalidomide and a proteasome inhibitor

The most commonly reported adverse reactions in clinical studies have been blood and lymphatic system disorders including anaemia (45,7 %), neutropenia (45,3 %) and thrombocytopenia (27 %); in general disorders and administration site conditions including fatigue (28,3 %), pyrexia (21 %) and oedema peripheral (13 %); and in infections and infestations including pneumonia (10,7 %). Peripheral neuropathy adverse reactions were reported in 12,3 % of patients and venous embolic or thrombotic (VTE) adverse reactions were reported in 3,3 % of patients. The most commonly reported Grade 3 or 4 adverse reactions were in the blood and lymphatic system disorders including neutropenia (41,7 %), anaemia (27 %) and thrombocytopenia (20,7 %); in infections and infestations including pneumonia (9 %); and in general disorders and administration site conditions including fatigue (4,7 %), pyrexia (3 %) and oedema peripheral (1,3 %). The most commonly reported serious adverse reaction was pneumonia (9,3 %). Other serious adverse reactions reported included febrile neutropenia (4,0 %), neutropenia (2,0 %), thrombocytopenia (1,7 %) and VTE adverse reactions (1,7 %).

Tabulated list of adverse reactions (ADR'S)

In randomised study CC-4047-MM-003, 302 patients with relapsed and refractory multiple myeloma were exposed to 4 mg pomalidomide administered once daily for 21 days of each 28 day cycle in combination with a weekly low dose of dexamethasone.

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

Frequencies are defined in accordance with current guidance, as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); and uncommon (≥ 1/1 000 to < 1/100).

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Infections and infestations	**Very Common** Pneumonia (bacterial, viral and fungal infections, including opportunistic infections) **Common** Neutropenic sepsis Bronchopneumonia Bronchitis Respiratory tract infection Upper respiratory tract infection Nasopharyngitis Herpes zoster **Not Known** Hepatitis B reactivation	**Common** Neutropenic sepsis Pneumonia (bacterial, viral and fungal infections, including opportunistic infections) Bronchopneumonia Respiratory tract infection Upper respiratory tract infection **Uncommon** Bronchitis Herpes zoster **Not Known** Hepatitis B reactivation
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**Uncommon** Basal cell carcinoma of the skin Squamous cell carcinoma of the skin	**Uncommon** Basal cell carcinoma of the skin Squamous cell carcinoma of the skin

Blood and lymphatic system disorders	**Very Common** Neutropenia Thrombocytopenia Leucopenia Anaemia **Common** Febrile neutropenia Pancytopenia*	**Very Common** Neutropenia Thrombocytopenia Anaemia **Common** Febrile neutropenia Leucopenia Pancytopenia*
Metabolism and nutrition disorders	**Very Common** Decreased appetite **Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Tumour lysis syndrome*	**Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Decreased appetite Tumour lysis syndrome*
Psychiatric disorders	**Common** Confusional state	**Common** Confusional state

Nervous system disorders	**Common** Depressed level of consciousness Peripheral sensory neuropathy Dizziness Tremor Intracranial haemorrhage* **Uncommon** Cerebrovascular accident*	**Common** Depressed level of consciousness **Uncommon** Peripheral sensory neuropathy Dizziness Tremor Cerebrovascular accident* Intracranial haemorrhage*
Ear and labyrinth disorders	**Common** Vertigo	**Common** Vertigo
Vascular disorders	**Common** Deep vein thrombosis	**Uncommon** Deep vein thrombosis
Cardiac disorders	**Common** Cardiac failure* Atrial fibrillation* Myocardial infarction*	**Common** Cardiac failure* Atrial fibrillation* **Uncommon** Myocardial infarction*
Immune system disorders	**Common** Angioedema* Urticaria*	**Uncommon** Angioedema* Urticaria*

Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea Cough **Common** Pulmonary embolism Epistaxis* Interstitial lung disease*	**Common** Dyspnoea **Uncommon** Pulmonary embolism Cough Epistaxis* Interstitial lung disease*
Gastrointestinal disorders	**Very Common** Diarrhoea Nausea Constipation **Common** Vomiting Gastrointestinal haemorrhage	**Common** Diarrhoea Vomiting Constipation **Uncommon** Nausea Gastrointestinal haemorrhage
Hepatobiliary disorders	**Uncommon** Hyperbilirubinaemia Hepatitis*	**Uncommon** Hyperbilirubinaemia

Skin and subcutaneous tissue disorders	**Common** Rash Pruritus	**Common** Rash
Musculoskeletal and connective tissue disorders	**Very Common** Bone pain Muscle spasms	**Common** Bone pain **Uncommon** Muscle spasms
Renal and urinary disorders	**Common** Renal failure Urinary retention	**Common** Renal failure **Uncommon** Urinary retention
Reproductive system and breast disorders	**Common** Pelvic pain	**Common** Pelvic pain
General disorders and administration site conditions	**Very Common** Fatigue Pyrexia Peripheral oedema	**Common** Pyrexia Fatigue Peripheral oedema

Investigations	**Common**	**Common**
	Decreased neutrophil count	Decreased neutrophil count
	Decreased white blood cell count	Decreased white blood cell count
	Decreased platelet count	Decreased platelet count
	Increased alanine aminotransferase	Increased alanine aminotransferase
	Increased blood uric acid increased*	
		Uncommon
		Increased blood uric acid increased*

* Identified from post marketing data, with frequencies based on clinical trial data

Pomalidomide Adverse Drug Reactions (ADRs) in Pediatric Patients with Recurrent or Progressive Brain Tumors

Adverse reactions reported in paediatric patients (aged 4 to 18 years) with recurrent or progressive brain tumors 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 IMNOVID.

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 hemorrhage.

*Hepatobiliary Disorders***:** Hepatitis, increased liver function tests.

I*mmune System Disorders***:** Allergic reactions (e.g. angioedema, anaphylaxis, urticaria).

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

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

Respiratory, Thoracic and Mediastinal Disorders: Interstitial lung disease (ILD), pneumonitis.
Skin and Subcutaneous Tissue Disorders: Stevens-Johnson Syndrome, toxic epidermal necrolysis, medicine reaction with eosinophilia and systemic symptoms (DRESS).

Description of selected adverse reactions

Teratogenicity:

IMNOVID 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 IMNOVID is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected (see section 4.4 Special warnings and precautions for use, section 4.6 Fertility, pregnancy and lactation).

Neutropenia and thrombocytopenia:

Neutropenia occurred in 45,3 % of patients who received pomalidomide plus low dose dexamethasone (Pom + LD-Dex), and in 19,5 % of patients who received high dose dexamethasone (HD-Dex). Neutropenia was Grade 3 or 4 in 41,7 % of patients who received Pom + LD-Dex, compared with 14,8 % who received HD-Dex. In Pom + LD-Dex treated patients
neutropenia was infrequently serious (2,0 % of patients), did not lead to treatment discontinuation, and was associated with treatment interruption in 21,0 % of patients, and with dose reduction in 7,7 % of patients.

Febrile neutropenia (FN) was experienced in 6,7 % of patients who received Pom + LD-Dex, and in no patients who received HD-Dex. All were reported to be Grade 3 or 4. FN was reported to be serious in 4,0 % of patients. FN was associated with dose interruption in 3,7 % of patients, and with dose reduction in 1,3 % of patients, and with no treatment discontinuations.

Thrombocytopenia occurred in 27,0 % of patients who received Pom + LD-Dex, and 26,8 % of patients who received HD-Dex. Thrombocytopenia was Grade 3 or 4 in 20.7% of patients who received Pom + LD-Dex and in 24,2 % who received HD-Dex. In Pom + LD-Dex treated patients, thrombocytopenia was serious in 1,7 % of patients, led to dose reduction in 6,3 % of patients, to dose interruption in 8 % of patients and to treatment discontinuation in 0,7 % of patients (see section 4.4 Special warnings and precautions for use, section 4.6 Fertility, pregnancy and lactation).

Infection:

Infection was the most common non haematological toxicity; it occurred in 55,0 % of patients who received Pom + LD-Dex, and 48,3 % of patients who received HD-Dex. Approximately half of those infections were Grade 3 or 4; 24,0 % in Pom + LD-Dex-treated patients and 22,8 % in patients who received HD-Dex.

In Pom + LD-Dex treated patients, pneumonia and upper respiratory tract infections were the most commonly reported infections (in 10,7 % and 9,3 % of patients, respectively); with 24,3 % of reported infections being serious and fatal infections (Grade 5) occurring in 2,7 % of treated patients. In Pom + LD-Dex treated patients infections led to dose discontinuation in 2,0 % of patients, to treatment interruption in 14,3 % of patients, and to a dose reduction in 1,3 % of patients.

Thromboembolic events:

Venous embolic or thrombotic events (VTE) occurred in 3,3 % of patients who received Pom + LD-Dex, and 2,0 % of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1,3 % of patients who received Pom + LD-Dex, and no patients who received HD-Dex. In Pom + LD-Dex treated patients, VTE

was reported as serious in 1,7 % of patients, no fatal reactions were reported in clinical studies, and VTE was not associated with dose discontinuation.

Prophylaxis with aspirin (and other anticoagulants in high risk patients) was mandatory for all patients in clinical studies. Anticoagulation therapy (unless contraindicated) is recommended (see section 4.2 Posology and method of administration)

Peripheral neuropathy:

Patients with ongoing peripheral neuropathy ≥ Grade 2 were excluded from clinical studies. Peripheral neuropathy, mostly Grade 1 or 2 occurred in 12,3 % patients who received Pom + LD-Dex, and 10,7 % of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1,0 % of patients who received Pom + LD-Dex and in 1,3 % of patients who received HD-Dex. In patients treated with Pom + LD-Dex, no peripheral neuropathy reactions were reported to have been serious in clinical trials and peripheral neuropathy led to dose discontinuation in 0,3 % of patients (see section 4.4 Special warnings and precautions for use, section 4.6 Fertility, pregnancy and lactation).

Haemorrhage:

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction 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 Undesirable effects).

Treatment should be symptomatic and supportive.

It is unknown whether pomalidomide or its metabolites are dialysable.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code:

Other immunosuppressants/ L04AX06

Mechanism of action:

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

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

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

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.

5.2 Pharmacokinetic properties

Absorption:

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

Co-administration with a high-fat and high-calorie meal slows the rate of absorption, decreasing plasma C_{max} by ~25 %, but has minimal effect on the overall extent of absorption with an 8 % decrease in AUC. Therefore, pomalidomide can be administered without regard to food intake.

Distribution:

Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67 % of plasma level at 4 hours post-dose (~T_{max}) after 4 days of once daily dosing at 4 mg. In vitro binding of pomalidomide enantiomers to proteins in human plasma ranges from 12 % to 44 % and is not concentration dependent.

Metabolism:

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

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

Co-administration of pomalidomide with the strong CYP3A4/5 (and P-gp inhibitor) ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide.

Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased exposure to pomalidomide by 104 % with a 90 % confidence interval [88 % to 122 %] compared to pomalidomide plus ketoconazole. 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).

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.

Excretion:

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).

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 tumor, the median T_{max} was 2 to 4 hours postdose 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 pediatric brain tumors. 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-∞) and Cmax 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

Mannitol, pregelatinised starch, sodium stearyl fumarate and a gelatin capsule shell.

Capsule shell:

1 mg capsule shell contains gelatin, titanium dioxide (E171), indigotine (E132) and yellow iron oxide (E172) and white and black ink.

2 mg capsule shell contains gelatin, titanium dioxide (E171), indigotine (E132), yellow iron oxide (E172), erythrosin (E127) and white ink.

3 mg capsule shell contains gelatin, titanium dioxide (E171), indigotine (E132), yellow iron oxide (E172), and white ink.

4 mg capsule shell contains gelatin, titanium dioxide (E171), indigotine (E132), brilliant blue FCF (E133) and white ink.

Printing ink:

1 mg capsule shell contains: white ink - shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527). Black ink - shellac, iron oxide black (E172), propylene glycol (E1520) and ammonium hydroxide (E527).

2 mg capsule shell contains: white ink – shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527).

3 mg capsule shell contains: white ink – shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527).

4 mg capsule shell contains: white ink – shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527).

4 mg capsule shell contains: white ink – shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original container until required for administration.

6.5 Nature and contents of container

Clear colourless polyvinylchloride (PVC) / Polychlorotrifluoroethylene (PCTFE) / Aluminium foil blisters.

The blisters are packed in a cardboard carton.

Each pack contains 21 capsules.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

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.

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

7 NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 Eleventh Avenue

Houghton Estate

2198

Johannesburg

8 REGISTRATION NUMBER(S)

Imnovid 1 mg - 49/32.2/0744

Imnovid 2 mg - 49/32.2/0745

Imnovid 3 mg - 49/32.2/0746

Imnovid 4 mg - 49/32.2/0747

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 May 2020

10 DATE OF REVISION OF TEXT

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Date of this variation: 29 March 2023

Signature  29 March 2023