SAMENVATTING VAN DE PRODUCTKENMERKEN

1. NAME OF THE MEDICINAL PRODUCT

Polidma 1 mg, harde capsules
Polidma 2 mg, harde capsules
Polidma 3 mg, harde capsules
Polidma 4 mg, harde capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[product name] 1 mg hard capsules

Each hard capsule contains 1 mg of pomalidomide.

[product name] 2 mg hard capsules

Each hard capsule contains 2 mg of pomalidomide.

[product name] 3 mg hard capsules

Each hard capsule contains 3 mg of pomalidomide.

[product name] 4 mg hard capsules

Each hard capsule contains 4 mg of pomalidomide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule)

[product name] 1 mg hard capsules
Hard gelatin capsule, with a yellow body and red cap, with “PLM 1” printed axial rectified in white in the body. Capsule size 4 (approximately 14.3 mm in length).

[product name] 2 mg hard capsules
Hard gelatin capsule, with an orange body and red cap, with “PLM 2” printed axial rectified in white in the body. Capsule size 2 (approximately 18 mm in length).

[product name] 3 mg hard capsules
Hard gelatin capsule, with a turquoise body and red cap, with “PLM 3” printed axial rectified in white in the body. Capsule size 2 (approximately 18 mm in length).

[product name] 4 mg hard capsules
Hard gelatin capsule, with a dark blue body and red cap, with “PLM 4” printed axial rectified in white in the body. Capsule size 2 (approximately 18 mm in length).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[product name] in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

[product name] in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

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

Dosing is continued or modified based upon clinical and laboratory findings (see section 4.4).

Posology

Pomalidomide in combination with bortezomib and dexamethasone
The recommended starting dose of pomalidomide is 4 mg taken orally once daily on Days 1 to 14 of repeated 21- day cycles.

Pomalidomide is administered in combination with bortezomib and dexamethasone, as shown in Table 1. The recommended starting dose of bortezomib is 1.3 mg/m^2 intravenous or subcutaneous once daily, on the days shown in Table 1. The recommended dose of dexamethasone is 20 mg taken orally once daily, on the days shown in Table 1.

Treatment with pomalidomide combined with bortezomib and dexamethasone should be given until disease progression or until unacceptable toxicity occurs.

Table 1: Recommended dosing scheme for pomalidomide in combination with bortezomib and dexamethasone

Cycle 1-8	Day (of 21-day cycle)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pomalidomide (4 mg)	•	•	•	•	•	•	•	•	•	•	•	•	•	•							
Bortezomib (1.3 mg/m^2)	•			•				•			•										
Dexamethasone (20 mg) *	•	•		•	•			•	•		•	•									

Cycle 9 onwards	Day (of 21-day cycle)																				
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Pomalidomide (4 mg)	•	•	•	•	•	•	•	•	•	•	•	•	•	•							
Bortezomib (1.3 mg/m^2)	•							•													
Dexamethasone (20 mg) *	•	•						•	•												

* For patients > 75 years of age, see Special populations.

Pomalidomide dose modification or interruption
To initiate a new cycle of pomalidomide, the neutrophil count must be ≥ 1 x 10^9/l and the platelet count must be ≥ 50 x 10^9/l.

Instructions on dose interruptions or reductions for pomalidomide related adverse reactions are outlined in the Table 2 and dose levels are defined in Table 3 below:

Table 2: Pomalidomide dose modification instructions∞

Toxicity	Dose modification
Neutropenia* ANC** < 0.5 x 10^9/l or febrile neutropenia (fever ≥38.5°C and ANC <1 x 10^9/l)	Interrupt pomalidomide treatment for remainder of cycle. Follow CBC*** weekly.
ANC return to ≥ 1 x 10^9/l	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop < 0.5 x 10^9/l	Interrupt pomalidomide treatment.
ANC return to ≥ 1 x 10^9/l	Resume pomalidomide treatment at one dose level lower than the previous dose.
Thrombocytopenia Platelet count < 25 x 10^9/l	Interrupt pomalidomide treatment for remainder of cycle. Follow CBC*** weekly.
Platelet count return to ≥ 50 x 10^9/l	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop < 25 x 10^9/l	Interrupt pomalidomide treatment.
Platelet count return to ≥ 50 x 10^9/l	Resume pomalidomide treatment at one dose level lower than the previous dose.
Rash Rash = Grade 2-3	Consider dose interruption or discontinuation of pomalidomide treatment.
Rash = Grade 4 or blistering (including angioedema, anaphylactic reaction, exfoliative or bullous rash or if Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected)	Permanently discontinue treatment (see section 4.4).
Other Other ≥ Grade 3 pomalidomide-related adverse events	Interrupt pomalidomide treatment for remainder of cycle. Resume at one dose level lower than previous dose at next cycle (adverse event must be resolved or improved to ≤ Grade 2 before restarting dosing).

∞ Dose modification instructions in this table are applicable to pomalidomide in combination with bortezomib and dexamethasone and to pomalidomide in combination with dexamethasone.
*In case of neutropenia, the physician should consider the use of growth factors.
**ANC – Absolute Neutrophil Count;
***CBC – Complete Blood Count.

Table 3: Pomalidomide dose reduction∞

Dose level	Oral pomalidomide dose
Starting dose	4 mg
Dose level -1	3 mg
Dose level -2	2 mg
Dose level -3	1 mg

∞Dose reduction in this table is applicable to pomalidomide in combination with bortezomib and dexamethasone and to pomalidomide in combination with dexamethasone.

If adverse reactions occur after dose reductions to 1 mg, then the treatment should be discontinued.

Strong CYP1A2 inhibitors
If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, the dose of pomalidomide should be reduced by 50% (see sections 4.5 and 5.2).

Bortezomib dose modification or interruption
For instructions on dose interruptions or reductions for bortezomib related adverse reactions, physicians should refer to bortezomib Summary of Product Characteristics (SmPC).

Dexamethasone dose modification or interruption
Instructions on dose interruptions or reductions for low-dose dexamethasone related adverse reactions are outlined in Tables 4 and 5 below. However, dose interruption or resumption decisions are at the physician's discretion per Summary of Product Characteristics (SmPC).

Table 4: Dexamethasone dose modification instructions

Toxicity	**Dose Modification**
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H_2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Interrupt dose until symptoms are controlled. Add H_2 blocker or equivalent and resume at one dose level lower than previous dose.
Oedema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. Resume at one dose level lower than previous dose.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Resume at one dose level lower than previous dose.
Hyperglycaemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed.
Acute pancreatitis	Discontinue dexamethasone from treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until the adverse event resolves to ≤ Grade 2. Resume at one dose level lower than previous dose.

If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be resumed at one dose level lower than the previous dose.

Table 5: Dexamethasone dose reduction

Dose Level	**≤ 75 years old** **Dose (Cycle 1-8: Days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle** **Cycle ≥ 9: Days 1, 2, 8, 9 of a 21-day cycle)**	**> 75 years old** **Dose (Cycle 1-8: Days 1, 2, 4, 5, 8, 9, 11, 12 of a 21-day cycle** **Cycle ≥ 9: Days 1, 2, 8, 9 of a 21-day cycle)**
Starting Dose	20 mg	10 mg
Dose Level -1	12 mg	6 mg
Dose Level -2	8 mg	4 mg

Dexamethasone should be discontinued if the patient is unable to tolerate 8 mg if ≤ 75 years old or 4 mg if > 75 years old.

In case of permanent discontinuation of any component of the treatment regimen, continuation of the remaining medicinal products is at the physician's discretion.

Pomalidomide in combination with dexamethasone
The recommended starting dose of pomalidomide is 4 mg taken orally once daily on Days 1 to 21 of each 28-day cycle.

The recommended dose of dexamethasone is 40 mg taken orally once daily on Days 1, 8, 15 and 22 of each 28-day cycle.

Treatment with pomalidomide combined with dexamethasone should be given until disease progression or until unacceptable toxicity occurs.

Pomalidomide dose modification or interruption
Instructions for dose interruptions or reductions for pomalidomide related adverse reactions are outlined in Table 2 and 3.

Dexamethasone dose modification or interruption
Instructions for dose modification for dexamethasone related adverse reactions are outlined in Table 4. Instructions for dose reduction for dexamethasone related adverse reactions are outlined in Table 6 below. However, dose interruption / resumption decisions are at physician's discretion per the current Summary of Product Characteristics (SmPC).

Table 6: Dexamethasone dose reduction

Dose Level	**≤ 75 years old** **Days 1, 8, 15 and 22 of each 28-day cycle**	**> 75 years old** **Days 1, 8, 15 and 22 of each 28-day cycle**
Starting Dose	40 mg	20 mg
Dose Level -1	20 mg	12 mg
Dose Level -2	10 mg	8 mg

Dexamethasone should be discontinued if the patient is unable to tolerate 10 mg if ≤ 75 years old or 8 mg if > 75 years old.

Special populations

Elderly
No dose adjustment is required for pomalidomide.

Pomalidomide in combination with bortezomib and dexamethasone
For patients >75 years of age, the starting dose of dexamethasone is:

- For Cycles 1 to 8: 10 mg once daily on Days 1, 2, 4, 5, 8, 9, 11 and 12 of each 21-day cycle
- For Cycles 9 and onwards: 10 mg once daily on Days 1, 2, 8 and 9 of each 21-day cycle.

Pomalidomide in combination with dexamethasone
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 cycle.

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 monitored for adverse reactions and dose reduction or interruption of pomalidomide should be used as needed.

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

Paediatric population
There is no relevant use of pomalidomide in children aged 0-17 years for the indication of multiple myeloma.
Outside its authorised indications, pomalidomide has been studied in children aged 4 to 18 years with recurrent or progressive brain tumours, however the results of studies did not allow to conclude that the benefits of such use outweigh the risks. Currently available data are described in sections 4.8, 5.1 and 5.2.

Method of administration

Oral use.
[product name] hard capsules should be taken orally at the same time each day. The capsules should not be opened, broken or chewed (see section 6.6). The capsules should be swallowed whole, preferably with water, with or without food. If the patient forgets to take a dose of pomalidomide on one day, then the patient should take the normal prescribed dose as scheduled on the next day. Patients should not adjust the dose to make up for a missing dose on previous days.

It is recommended to press only on one end of the capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.

4.3 Contraindications

- Pregnancy.
- Women of childbearing potential, unless all the conditions of the pregnancy prevention 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).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Teratogenicity

Pomalidomide 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. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis (see section 5.3).

The conditions of the Pregnancy Prevention 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 ≥ 1 year (amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential)
- Premature ovarian failure confirmed by a specialist gynaecologist
- Previous bilateral salpingo-oophorectomy, or hysterectomy
- XY genotype, Turner syndrome, uterine agenesis.

Counselling

For women of childbearing potential, pomalidomide 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 pomalidomide.

The prescriber must ensure that for women of childbearing potential:

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

For male patients taking pomalidomide, 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 pomalidomide 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, during dose interruption and for 7 days after dose interruptions and/or cessation of treatment. This includes vasectomised males who should wear a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential as seminal fluid may still contain pomalidomide in the absence of spermatozoa.
- He understands that if his female partner becomes pregnant whilst he is taking pomalidomide or 7 days after he has stopped taking pomalidomide, he should inform his treating physician immediately and that it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice.

Contraception

Women of childbearing potential must use at least one effective method of contraception for at least 4 weeks before therapy, during therapy, and until at least 4 weeks after pomalidomide 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:

- Implant
- Levonorgestrel-releasing intrauterine system
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

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 cotreatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Insertion of copper-releasing intrauterine devices is not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with severe neutropenia or severe thrombocytopenia.

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 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 pomalidomide to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment
A medically supervised pregnancy test should be performed during the consultation, when pomalidomide is prescribed, or in the 3 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with pomalidomide.

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 3 days prior to the visit to the prescriber.

Additional precautions

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

Patients should not donate blood, semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of pomalidomide.

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 pomalidomide, to provide advice on contraception before treatment is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform the patient about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool as agreed with each National Competent Authority. In collaboration with each National Competent Authority, a controlled access program has been implemented which includes the use of a patient card and/or equivalent tool for prescribing and /or dispensing controls, and the collection of information relating to the indication in order to monitor the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of pomalidomide to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result. Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks according to the approved indications dosing regimens (see section 4.2), and prescriptions for all other patients can be for a maximum duration of 12 weeks.

Haematological events

Neutropenia was the most frequently reported Grade 3 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. Physicians should observe patients for signs of bleeding including epistaxes, 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 pomalidomide either in combination with bortezomib and dexamethasone or in combination with dexamethasone have developed venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) and arterial thrombotic events (myocardial infarction and cerebrovascular accident) (see section 4.8). 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 physicians 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 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

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). Physicians 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 SJS, TEN and DRESS have been reported with the use of pomalidomide (see section 4.8). Patients should be advised of the signs and symptoms of these reactions by their prescribers and should be told to seek medical attention immediately if they develop these symptoms. Pomalidomide must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Patients with a prior history of serious allergic reactions associated with thalidomide or lenalidomide were excluded from clinical studies. Such patients may be at higher risk of hypersensitivity reactions and should not receive pomalidomide. Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued permanently for angioedema and anaphylactic reaction.

Dizziness and confusion

Dizziness and confusional state have been reported with pomalidomide. Patients must avoid situations where dizziness or confusion may be a problem and not to take other medicinal products that may cause dizziness or confusion without first seeking medical advice.

Interstitial lung disease (ILD)

ILD and related events, including cases of pneumonitis, have been observed with pomalidomide. Careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. Pomalidomide should be interrupted pending investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and the risks.

Hepatic disorders

Markedly elevated levels of alanine aminotransferase and bilirubin have been observed in patients treated with pomalidomide (see section 4.8). There have also been cases of hepatitis that resulted in discontinuation of pomalidomide. Regular monitoring of liver function is recommended for the first 6 months of treatment with pomalidomide and as clinically indicated thereafter.

Infections

Reactivation of hepatitis B has been reported rarely in patients receiving pomalidomide in combination with dexamethasone who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure, resulting in discontinuation of pomalidomide. Hepatitis B virus status should be established before initiating treatment with pomalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when pomalidomide in combination with dexamethasone is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Progressive multifocal leukoencephalopathy (PML)

Cases of progressive multifocal leukoencephalopathy, including fatal cases, have been reported with pomalidomide. PML was reported several months to several years after starting the treatment with pomalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Physicians should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

The evaluation for PML should be based on neurological examination, magnetic resonance imaging of the brain, and cerebrospinal fluid analysis for JC virus (JCV) DNA by polymerase chain reaction (PCR) or a brain biopsy with testing for JCV. A negative JCV PCR does not exclude PML. Additional follow-up and evaluation may be warranted if no alternative diagnosis can be established.

If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed, pomalidomide must be permanently discontinued.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of pomalidomide on other medicinal products

Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic 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 interactions, including the potential impact of pomalidomide on the pharmacokinetics of combined oral contraceptives, has not been evaluated clinically (see section 4.4 Teratogenicity).

Effect of other medicinal products on pomalidomide

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 mean 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 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

Dexamethasone

Co-administration of multiple doses of up to 4 mg pomalidomide 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.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with pomalidomide, treatment must be stopped and the patient should be referred to a physician specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking pomalidomide, it is recommended to refer the female partner to a physician specialised or experienced in teratology for evaluation and advice. Pomalidomide is present in human semen. As a precaution, all male patients taking pomalidomide should use condoms throughout treatment duration, during dose interruption and for 7 days 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. Pomalidomide is contraindicated during pregnancy and in women of childbearing potential, except when all the conditions for pregnancy prevention have been met (see sections 4.3 and 4.4).

Breast-feeding

It is unknown whether pomalidomide is excreted in human milk. Pomalidomide was detected in milk of lactating rats following administration to the mother. Because of the potential for adverse reactions in breastfed infants from pomalidomide, a decision must be made whether to discontinue breast-feeding or to discontinue the medicinal product, taking into account the benefit of breast-feeding for the child and the benefit of the therapy for the woman.

Fertility

Pomalidomide was found to impact negatively on fertility and be teratogenic in animals. Pomalidomide crossed the placenta and was detected in foetal blood following administration to pregnant rabbits (see section 5.3).

4.7 Effects on ability to drive and use machines

Pomalidomide has minor or moderate influence on the ability to drive and use machines. Fatigue, depressed level of consciousness, confusion, and dizziness have been reported with the use of pomalidomide. If affected, patients should be instructed not to drive cars, use machines or perform hazardous tasks while being treated with pomalidomide.

4.8 Undesirable effects

Summary of the safety profile

Pomalidomide in combination with bortezomib and dexamethasone
The most commonly reported blood and lymphatic system disorders were neutropenia (54.0%), thrombocytopenia (39.9%) and anaemia (32.0%). Other most frequently reported adverse reactions included peripheral sensory neuropathy (48.2%), fatigue (38.8%), diarrhoea (38.1%), constipation (38.1%), and oedema peripheral (36.3%). The most commonly reported Grade 3 or 4 adverse reactions were blood and lymphatic system disorders including neutropenia (47.1%), thrombocytopenia (28.1%) and anaemia (15.1%). The most commonly reported serious adverse reaction was pneumonia (12.2%). Other serious adverse reactions reported included pyrexia (4.3%), lower respiratory tract infection (3.6%), influenza (3.6%), pulmonary embolism (3.2%), atrial fibrillation (3.2%), and acute kidney injury (2.9%).

Pomalidomide in combination with dexamethasone
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 %).

Adverse reactions tended to occur more frequently within the first 2 cycles of treatment with pomalidomide.

Tabulated list of adverse reactions

The adverse reactions observed in patients treated with pomalidomide in combination with bortezomib and dexamethasone, pomalidomide in combination with dexamethasone and from post-marketing surveillance are listed in Table 7 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) and not known (frequency cannot be determined).

Table 7: Adverse reactions (ADRs) reported in clinical trials and post-market settings

Combination of treatment	**Pomalidomide/ bortezomib/dexamethasone**		**Pomalidomide/ dexamethasone**	
System Organ Class /Preferred term	**All ADRs**	**Grade 3-4 ADRs**	**All ADRs**	**Grade 3-4 ADRs**
Infections and infestations				
Pneumonia	Very common	Very common	-	-
Pneumonia (bacterial, viral and fungal infections, including opportunistic infections)	-	-	Very common	Common
Bronchitis	Very common	Common	Common	Uncommon

Combination of treatment	Pomalidomide/ bortezomib/dexamethasone		Pomalidomide/ dexamethasone	
System Organ Class /Preferred term	**All ADRs**	**Grade 3-4 ADRs**	**All ADRs**	**Grade 3-4 ADRs**
Upper respiratory tract infection	Very common	Common	Common	Common
Viral upper respiratory tract infection	Very common	-	-	-
Sepsis	Common	Common	-	-
Septic shock	Common	Common	-	-
Neutropenic sepsis	-	-	Common	Common
Clostridium difficile colitis	Common	Common	-	-
Bronchopneumonia	-	-	Common	Common
Respiratory tract infection	Common	Common	Common	Common
Lower respiratory tract infection	Common	Common	-	-
Lung infection	Common	Uncommon	-	-
Influenza	Very common	Common	-	-
Bronchiolitis	Common	Common	-	-
Urinary tract infection	Very common	Common	-	-
Nasopharyngitis	-	-	Common	-
Herpes zoster	-	-	Common	Uncommon
Hepatitis B reactivation	-	-	Not known*	Not known*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Basal cell carcinoma	Common	Uncommon	-	-
Basal cell carcinoma of the skin	-	-	Uncommon	Uncommon
Squamous cell carcinoma of the skin	-	-	Uncommon	Uncommon
Blood and lymphatic system disorders				
Neutropenia	Very common	Very common	Very common	Very common
Thrombocytopenia	Very common	Very common	Very common	Very common
Leucopenia	Very common	Common	Very common	Common
Anaemia	Very common	Very common	Very common	Very common
Febrile neutropenia	Common	Common	Common	Common
Lymphopenia	Common	Common	-	-
Pancytopenia	-	-	Common*	Common*
Immune system disorders				
Angioedema	-	-	Common*	Uncommon*
Urticaria	-	-	Common*	Uncommon*
Anaphylactic reaction	Not known*	Not known*	-	-
Solid organ transplant rejection	Not known*	-	-	-
Endocrine disorders				
Hypothyroidism	Uncommon*	-	-	-
Metabolism and nutrition disorders				
Hypokalaemia	Very common	Common	-	-
Hyperglycaemia	Very common	Common	-	-
Hypomagnesaemia	Common	Common	-	-
Hypocalcaemia	Common	Common	-	-
Hypophosphataemia	Common	Common	-	-
Hyperkalaemia	Common	Common	Common	Common
Hypercalcaemia	Common	Common	-	-

Combination of treatment	Pomalidomide/ bortezomib/dexamethasone		Pomalidomide/ dexamethasone	
System Organ Class /Preferred term	**All ADRs**	**Grade 3-4 ADRs**	**All ADRs**	**Grade 3-4 ADRs**
Hyponatraemia	-	-	Common	Common
Decreased appetite	-	-	Very common	Uncommon
Hyperuricaemia	-	-	Common*	Common*
Tumour lysis syndrome	-	-	Uncommon*	Uncommon*
Psychiatric disorders				
Insomnia	Very common	Common	-	-
Depression	Common	Common	-	-
Confusional state	-	-	Common	Common
Nervous system disorders				
Peripheral sensory neuropathy	Very common	Common	Common	Uncommon
Dizziness	Very common	Uncommon	Common	Uncommon
Tremor	Very common	Uncommon	Common	Uncommon
Syncope	Common	Common	-	-
Peripheral sensorimotor neuropathy	Common	Common	-	-
Paraesthesia	Common	-	-	-
Dysgeusia	Common	-	-	-
Depressed level of consciousness	-	-	Common	Common
Intracranial haemorrhage	-	-	Common*	Uncommon*
Cerebrovascular accident	-	-	Uncommon*	Uncommon*
Eye disorders				
Cataract	Common	Common	-	-
Ear and labyrinth disorders				
Vertigo	-	-	Common	Common
Cardiac disorders				
Atrial fibrillation	Very common	Common	Common*	Common*
Cardiac failure	-	-	Common*	Common*
Myocardial infarction	-	-	Common*	Uncommon*
Vascular disorders				
Deep vein thrombosis	Common	Uncommon	Common	Uncommon
Hypotension	Common	Common	-	-
Hypertension	Common	Common	-	-
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	Very common	Common	Very common	Common
Cough	Very common	-	Very common	Uncommon
Pulmonary embolism	Common	Common	Common	Uncommon
Epistaxis	-	-	Common*	Uncommon*
Interstitial lung disease	-	-	Common*	Uncommon*
Gastrointestinal disorders				
Diarrhoea	Very common	Common	Very common	Common
Vomiting	Very common	Common	Common	Common
Nausea	Very common	Uncommon	Very common	Uncommon
Constipation	Very common	Common	Very common	Common
Abdominal pain	Very common	Common	-	-
Abdominal pain upper	Common	Uncommon	-	-
Stomatitis	Common	Uncommon	-	-
Dry mouth	Common	-	-	-

Combination of treatment	Pomalidomide/ bortezomib/dexamethasone		Pomalidomide/ dexamethasone	
System Organ Class /Preferred term	**All ADRs**	**Grade 3-4 ADRs**	**All ADRs**	**Grade 3-4 ADRs**
Abdominal distension	Common	Uncommon	-	-
Gastrointestinal haemorrhage	-	-	Common	Uncommon
Hepatobiliary disorders				
Hyperbilirubinaemia	-	-	Uncommon	Uncommon
Hepatitis	-	-	Uncommon*	-
Skin and subcutaneous tissue disorders				
Rash	Very common	Common	Common	Common
Pruritus	-	-	Common	-
Drug Reaction with Eosinophilia and Systemic Symptoms	-	-	Not known*	Not known*
Toxic Epidermal Necrolysis	-	-	Not known*	Not known*
Stevens-Johnson Syndrome	-	-	Not known*	Not known*
Musculoskeletal and connective tissue disorders				
Muscular weakness	Very common	Common	-	-
Back pain	Very common	Common	-	-
Bone pain	Common	Uncommon	Very common	Common
Muscle spasms	Very common	-	Very common	Uncommon
Renal and urinary disorders				
Acute kidney injury	Common	Common	-	-
Chronic kidney injury	Common	Common	-	-
Urinary retention	Common	Common	Common	Uncommon
Renal failure	-	-	Common	Common
Reproductive system and breast disorders				
Pelvic pain	-	-	Common	Common
General disorders and administration site conditions				
Fatigue	Very common	Common	Very common	Common
Pyrexia	Very common	Common	Very common	Common
Oedema peripheral	Very common	Common	Very common	Common
Non-cardiac chest pain	Common	Common	-	-
Oedema	Common	Common	-	-
Investigations				
Alanine aminotransferase increased	Common	Common	Common	Common
Weight decreased	Common	Common	-	-
Neutrophil count decreased	-	-	Common	Common
White blood cell count decreased	-	-	Common	Common
Platelet count decreased	-	-	Common	Common
Blood uric acid increased	-	-	Common*	Uncommon*
Injury, poisoning and procedural complications				
Fall	Common	Common	-	-

* Reported during post-marketing use.

Description of selected adverse reactions

The frequencies in this section are from clinical studies in patients receiving pomalidomide treatment in combination either with bortezomib and dexamethasone (Pom+Btz+Dex) or with dexamethasone (Pom+Dex).

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 (see sections 4.6 and 5.3). If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected (see section 4.4).

Neutropenia and thrombocytopenia
Neutropenia occurred in up to 54.0% (Pom+Btz+Dex) patients (47.1% (Pom+Btz+Dex) Grade 3 or 4). Neutropenia led to pomalidomide discontinuation in 0.7% of patients and was infrequently serious.

Febrile neutropenia (FN) was reported in 3.2% (Pom+Btz+Dex) patients and 6.7% (Pom+Dex) patients and was serious in 1.8% (Pom+Btz+Dex) patients and 4.0% (Pom+Dex) patients (see sections 4.2 and 4.4).

Thrombocytopenia occurred in 39.9% (Pom+Btz+Dex) patients and 27.0% (Pom+Dex) patients. Thrombocytopenia was Grade 3 or 4 in 28.1% (Pom+Btz+Dex) patients and 20.7% (Pom+Dex) patients, led to pomalidomide discontinuation in 0.7% (Pom+Btz+Dex) patients and 0.7% (Pom+Dex) patients, and was serious in 0.7% (Pom+Btz+Dex) and 1.7% (Pom+Dex) of patients (see sections 4.2 and 4.4).

Neutropenia and thrombocytopenia tended to occur more frequently within the first 2 cycles of treatment with pomalidomide in combination either with bortezomib and dexamethasone or with dexamethasone.

Infection
Infection was the most common non haematological toxicity.

Infection occurred in 83.1% (Pom+Btz+Dex) patients and 55.0% (Pom+Dex) patients (34.9% (Pom+Btz+Dex) and 24.0% (Pom+Dex) Grade 3 or 4). Upper respiratory tract infection and pneumonia were the most frequently occurring infections. Fatal infections (Grade 5) occurred in 4.0% (Pom+Btz+Dex) patients and 2.7% (Pom+Dex) patients. Infections led to pomalidomide discontinuation in 3.6% (Pom+Btz+Dex) patients and 2.0% (Pom+Dex) patients.

Thromboembolic events
Prophylaxis with acetylsalicylic acid (and other anticoagulants in high risk patients) was mandatory for all patients in clinical studies. Anticoagulation therapy (unless contraindicated) is recommended (see section 4.4).

Venous thromboembolic events (VTE) occurred in 12.2% (Pom+Btz+Dex) and 3.3% (Pom+Dex) patients (5.8% (Pom+Btz+Dex) and 1.3% (Pom+Dex) Grade 3 or 4). VTE was reported as serious in 4.7% (Pom+Btz+Dex) and 1.7% (Pom+Dex) patients, no fatal reactions were reported, and VTE was associated with pomalidomide discontinuation in up to 2.2% (Pom+Btz+Dex) of patients.

Peripheral neuropathy - Pomalidomide in combination with bortezomib and dexamethasone
Patients with ongoing peripheral neuropathy ≥ Grade 2 with pain within 14 days prior to randomisation were excluded from clinical trials. Peripheral neuropathy occurred in 55.4% of patients (10.8% Grade 3; 0.7% Grade 4). Exposure-adjusted rates were comparable across treatment arms.
Approximately 30% of the patients experiencing peripheral neuropathy had a history of neuropathy at baseline. Peripheral neuropathy led to discontinuation of bortezomib in approximately 14.4% of patients, pomalidomide in 1.8% and dexamethasone in 1.8% of patients in the Pom+Btz+Dex arm and 8.9% of patients in the Btz+Dex arm.

Peripheral neuropathy - Pomalidomide in combination with dexamethasone
Patients with ongoing peripheral neuropathy ≥ Grade 2 were excluded from clinical studies. Peripheral neuropathy occurred in 12.3% of patients (1.0% Grade 3 or 4). No peripheral neuropathy reactions were reported as serious, and peripheral neuropathy led to dose discontinuation in 0.3% of patients (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 were 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Pomalidomide doses as high as 50 mg as a single dose in healthy volunteers have been studied without reporting serious adverse reactions related to overdose. Doses as high as 10 mg once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse reactions related to overdose. The dose-limiting toxicity was myelosuppression. In studies, pomalidomide was found to be removed by haemodialysis.

In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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), cullin 4 (CUL4), and regulator of cullins-1 (Roc1), and can inhibit the auto-ubiquitination of CRBN within the complex. E3 ubiquitin ligases are responsible for the poly-ubiquitination of a variety of substrate proteins, and may partially explain the pleiotropic cellular effects observed with pomalidomide treatment.

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.

Clinical efficacy and safety

Pomalidomide in combination with bortezomib and dexamethasone
The efficacy and safety of pomalidomide in combination with bortezomib and low-dose dexamethasone (Pom+Btz+LD-Dex) was compared with bortezomib and low-dose dexamethasone (Btz+LD-Dex) in a Phase III multi-centre, randomised, open-label study (CC-4047-MM-007), in previously treated adult patients with multiple myeloma, who had received at least one prior regimen, including lenalidomide and have demonstrated disease progression on or after the last therapy. A total of 559 patients were enrolled and randomised in the study: 281 in the Pom+Btz+LD-Dex arm and 278 in the Btz+LD-Dex arm. 54% of patients were male with median age for the overall population of 68 years (min, max: 27, 89 years). Approximately 70% of patients were refractory to lenalidomide (71.2% in Pom+Btz+LD-Dex, 68.7% in Btz+LD-Dex). Approximately 40% of patients were in 1st relapse and approximately 73% of patients received bortezomib as prior treatment.

Patients in the Pom+Btz+LD-Dex arm were administered 4 mg pomalidomide orally on Days 1 to 14 of each 21-day cycle. Bortezomib (1.3 mg/m^2/dose) was administered to patients in both study arms on Days 1, 4, 8 and 11 of a 21-day cycle for Cycles 1 to 8; and on Days 1 and 8 of a 21-day cycle for Cycles 9 and onwards. Low-dose dexamethasone (20 mg/day [≤ 75 years old] or 10 mg/day [> 75 years old]) was administered to patients in both study arms on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle for Cycles 1 to 8; and on Days 1, 2, 8 and 9 of each subsequent 21-day cycle from Cycles 9 onwards. Doses were reduced and treatment was temporarily interrupted or stopped as needed to manage toxicity (see section 4.2).

The primary efficacy endpoint was Progression Free Survival (PFS) assessed by an Independent Response Adjudication Committee (IRAC) according to the IMWG criteria using the intent to treat population (ITT). After a median follow-up of 15.9 months, median PFS time was 11.20 months (95% CI: 9.66, 13.73) in the Pom+Btz+LD-Dex arm. In the Btz+LD-Dex arm, median PFS time was 7.1 months (95% CI: 5.88, 8.48).

Summary of overall efficacy data are presented in Table 8 using a cut-off date of 26 Oct 2017.
Kaplan-Meier curve for PFS for the ITT population is provided in Figure 1.

Table 8: Summary of overall efficacy data

	Pom+Btz+LD-Dex (N = 281)	Btz+LD-Dex (N = 278)
PFS (months)		
Median [a] time (95% CI) [b]	11.20 (9.66, 13.73)	7.10 (5.88, 8.48)
HR [c] (95% CI), p-value [d]	0.61 (0.49, 0.77), <0.0001	
ORR, n (%)	82.2%	50.0%
sCR	9 (3.2)	2 (0.7)
CR	35 (12.5)	9 (3.2)
VGPR	104 (37.0)	40 (14.4)
PR	83 (29.5)	88 (31.7)
OR (95% CI) [e], p-value[f]	5.02 (3.35, 7.52), <0.001	
DoR (months)		
Median[a] time (95% CI) [b]	13.7 (10.94, 18.10)	10.94 (8.11, 14.78)
HR[c] (95% CI)	0.76 (0.56, 1.02)	

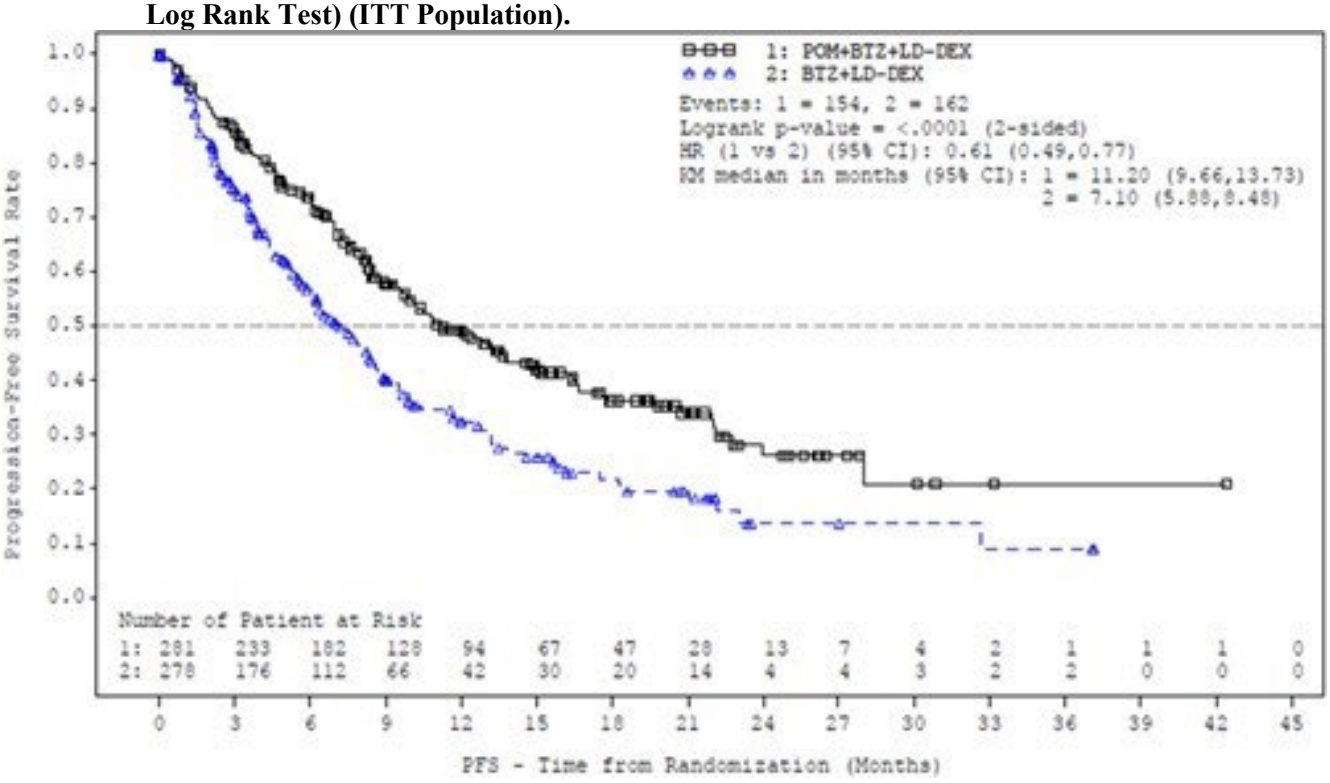
Btz = bortezomib; CI = Confidence interval; CR = Complete response; DoR = Duration of response; HR = Hazard Ratio; LD-Dex = low-dose dexamethasone; OR = Odds ratio; ORR = Overall response rate; PFS = Progression free survival; POM = pomalidomide; PR = Partial Response; sCR = Stringent complete response VGPR = Very good partial response.
[a] The median is based on the Kaplan-Meier estimate.
[b] 95% CI about the median.
[c] Based on Cox proportional hazards model.
[d] The p-value is based on a stratified log-rank test.

[e] Odds ratio is for Pom+Btz+LD-Dex:Btz+LD-Dex.
[f] The p-value is based on a CMH test, stratified by age (<=75 vs >75), Prior number of antimyeloma regimens (1 vs >1), and Beta-2 microglobulin at screening (< 3.5 mg/L versus ≥ 3.5 mg/L — ≤ 5.5 mg/L versus > 5.5 mg/L).

The median duration of treatment was 8.8 months (12 treatment cycles) in the Pom+Btz+LD-Dex arm and 4.9 months (7 treament cycles) in the Btz+LD-Dex arm.

The PFS advantage was more pronounced in patients who received only one prior line of therapy. In patients who received 1 prior antimyeloma line, median PFS time was 20.73 months (95% CI: 15.11, 27.99) in the Pom + Btz + LD-Dex arm and 11.63 months (95% CI: 7.52, 15.74) in the Btz + LD-Dex arm. A 46% risk reduction was observed with Pom + Btz + LD-Dex treatment (HR = 0.54, 95% CI: 0.36, 0.82).

Figure 1: Progression Free Survival based on IRAC Review of Response by IMWG Criteria (Stratified Log Rank Test) (ITT Population).



Data cutoff: 26 Oct 2017

Final analysis for Overall Survival (OS), using a cut-off of 13 May 2022 (median follow-up period of 64.5 months), median OS time from Kaplan-Meier estimates was 35.6 months for the Pom + Btz + LD-Dex arm and 31.6 months for the Btz + LD-Dex arm; HR = 0.94, 95% CI: -0.77, 1.15, with an overall event rate of 70.0%. The OS analysis was not adjusted to account for subsequent therapies received.

Pomalidomide in combination with dexamethasone
The efficacy and safety of pomalidomide in combination with dexamethasone were evaluated in a Phase III multi-centre, randomised, open-label study (CC-4047-MM-003), where pomalidomide plus low-dose dexamethasone therapy (Pom+LD-Dex) was compared to high-dose dexamethasone alone (HD-Dex) in previously treated adult patients with relapsed and refractory multiple myeloma, who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. A total of 455 patients were enrolled in the study: 302 in the Pom+LD-Dex arm and 153 in the HD-Dex arm. The majority of patients were male (59%) and white (79%); the median age for the overall population was 64 years (min, max: 35, 87 years).

Patients in the Pom+LD-Dex arm were administered 4 mg pomalidomide orally on days 1 to 21 of each 28-day cycle. LD-Dex (40 mg) was administered once per day on days 1, 8, 15 and 22 of a 28-day cycle. For the HD-Dex arm, dexamethasone (40 mg) was administered once per day on days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle. Patients > 75 years of age started treatment with 20 mg dexamethasone. Treatment continued until patients had disease progression.

The primary efficacy endpoint was progression free survival by International Myeloma Working Group (IMWG criteria). For the intention to treat (ITT) population, median PFS time by Independent Review Adjudication Committee (IRAC) review based on IMWG criteria was 15.7 weeks (95% CI: 13.0, 20.1) in the Pom + LD-Dex arm; the estimated 26-week event-free survival rate was 35.99% (±3.46%). In the HD-Dex arm, median PFS time was 8.0 weeks (95% CI: 7.0, 9.0); the estimated 26-week event-free survival rate was 12.15% (±3.63%).

PFS was evaluated in several relevant subgroups: gender, race, ECOG performance status, stratification factors (age, disease population, prior anti-myeloma therapies [2, > 2]), selected parameters of prognostic significance (baseline beta-2 microglobulin level, baseline albumin levels, baseline renal impairment, and cytogenetic risk), and exposure and refractoriness to prior anti-myeloma therapies. Regardless of the subgroup evaluated, PFS was generally consistent with that observed in the ITT population for both treatment groups.

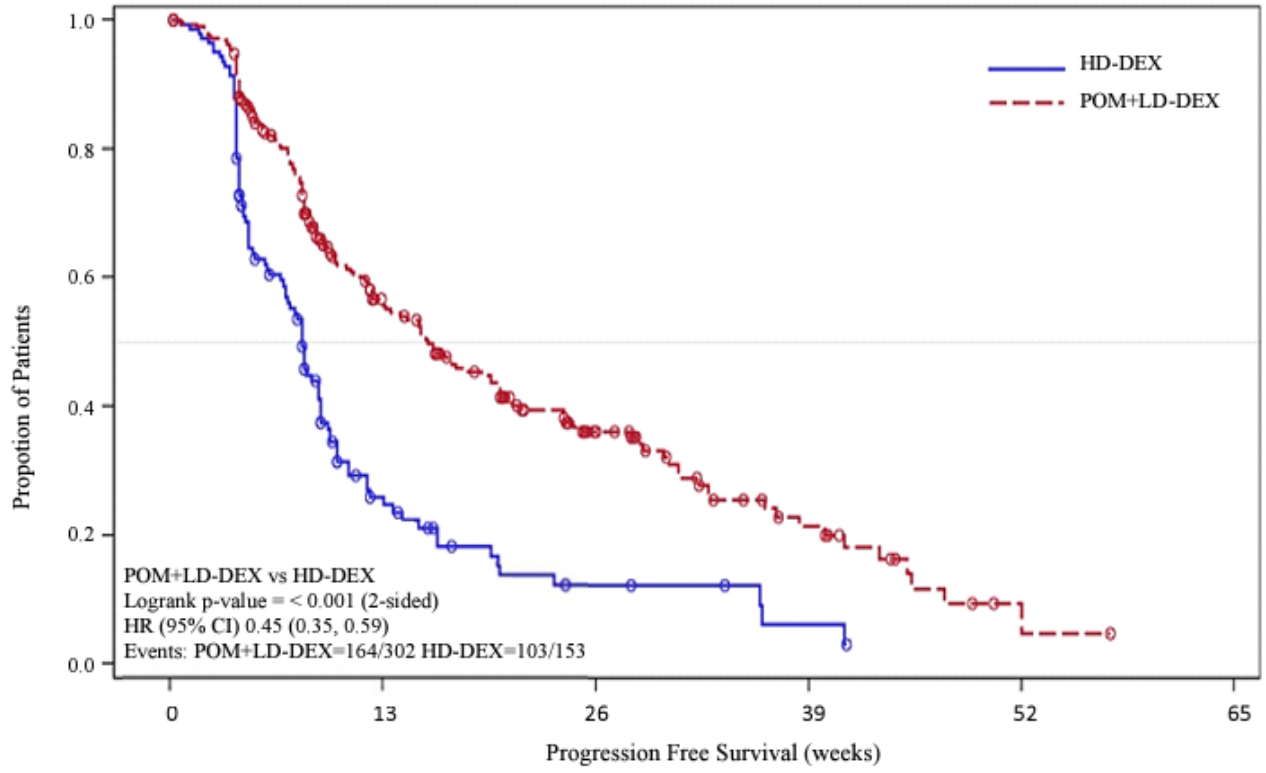
PFS is summarised in Table 9 for the ITT population. Kaplan-Meier curve for PFS for the ITT population is provided in Figure 2.

Table 9: Progression Free Survival Time by IRAC Review Based on IMWG Criteria (Stratified Log Rank Test) (ITT Population)

	Pom+LD-Dex (N=302)	**HD-Dex (N=153)**
Progression free survival (PFS), N	302 (100.0)	153 (100.0)
Censored, n (%)	138 (45.7)	50 (32.7)
Progressed/Died, n (%)	164 (54.3)	103 (67.3)
Progression Free Survival Time (weeks)		
Median[a]	15.7	8.0
Two sided 95% CI[b]	[13.0, 20.1]	[7.0, 9.0]
Hazard Ratio (Pom+LD-Dex:HD-Dex) 2-Sided 95% CI [c]	0.45 [0.35,0.59]	
Log-Rank Test Two sided P-Value [d]	<0.001	

Note: CI=Confidence interval; IRAC=Independent Review Adjudication Committee; NE = Not Estimable.
[a] The median is based on Kaplan-Meier estimate.
[b] 95% confidence interval about the median progression free survival time.
[c] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups, stratified by age (≤75 vs >75),diseases population (refractory to both lenalidomide and bortezomib vs not refractory to both active substances), and prior number of anti myeloma therapy (=2 vs >2).
[d] The p-value is based on a stratified log-rank test with the same stratification factors as the above Cox model.
Data cutoff: 07 Sep 2012

Figure 2: Progression Free Survival Based on IRAC Review of Response by IMWG Criteria (Stratified Log Rank Test) (ITT Population)



Data cutoff: 07 Sep 2012

Overall Survival was the key secondary study endpoint. A total of 226 (74.8%) of the Pom + LD-Dex patients and 95 (62.1%) of the HD-Dex patients were alive as of the cutoff date (07 Sep 2012). Median OS time from Kaplan-Meier estimates has not been reached for the Pom + LD-Dex, but would be expected to be at least 48 weeks, which is the lower boundary of the 95% CI. Median OS time for the HD-Dex arm was 34 weeks (95% CI: 23.4, 39.9). The 1-year event free rate was 52.6% (± 5.72%) for the Pom + LD-Dex arm and 28.4% (± 7.51%) for the HD-Dex arm. The difference in OS between the two treatment arms was statistically significant ($p < 0.001$).

Overall survival is summarised in Table 10 for the ITT population. Kaplan-Meier curve for OS for the ITT population is provided in Figure 3.

Based on the results of both PFS and OS endpoints, the Data Monitoring Committee established for this study recommended that the study be completed and patients in the HD-Dex arm be crossed over to the Pom + LD-Dex arm.

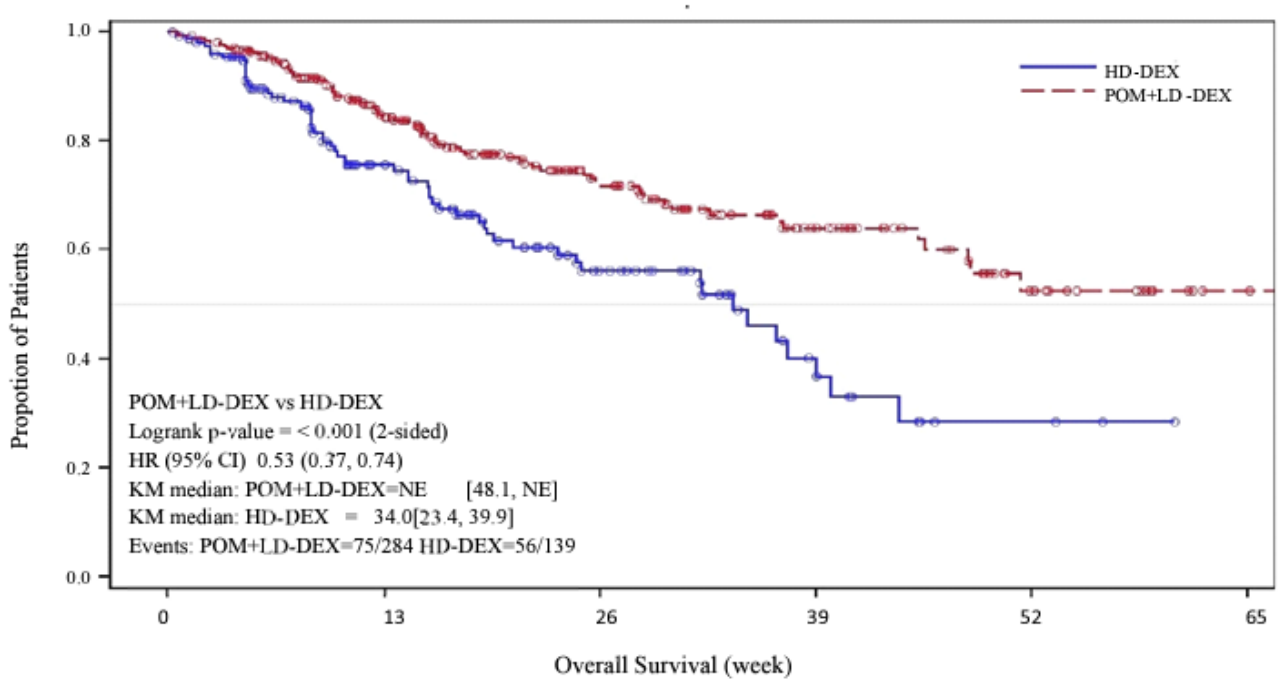
Table 10: Overall Survival: ITT Population

	Statistics	**Pom+LD-Dex (N=302)**	**HD-Dex (N=153)**
	N	302 (100.0)	153 (100.0)
Censored	n (%)	226 (74.8)	95 (62.1)
Died	n (%)	76 (25.2)	58 (37.9)
Survival Time (weeks)	Median[a]	NE	34.0
	Two sided 95% CI[b]	[48.1, NE]	[23.4, 39.9]
Hazard Ratio (Pom+LD-Dex:HD-Dex) [Two sided 95% CI[c]]		0.53[0.37, 0.74]	

	Statistics	Pom+LD-Dex (N=302)	HD-Dex (N=153)
Log-Rank Test Two sided P-Value[d]		<0.001	

Note: CI=Confidence interval. NE = Not Estimable.
[a] The median is based on Kaplan-Meier estimate.
[b] 95% confidence interval about the median overall survival time.
[c] Based on Cox proportional hazards model comparing the hazard functions associated with treatment groups.
[d] The p-value is based on an unstratified log-rank
test. Data cutoff: 07 Sep 2012

Figure 3: Kaplan-Meier Curve of Overall Survival (ITT Population)



cutoff: 07 Sep 2012

Paediatric population

In a Phase 1 single-arm, open-label, dose escalation study, the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) 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.
Efficacy was not demonstrated in a Phase 2 multi-centre, 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 central nervous system (CNS).
In the Phase 2 study, two patients in the high-grade glioma group (N=19) achieved a response as defined by protocol; one of these patients achieved a partial response (PR) and the other patient achieved a long term stable disease (SD), which resulted in an objective response (OR) and long-term SD rate of 10.5% (95% CI: 1.3, 33.1). One patient in the ependymoma group (N=9) achieved 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 any of the evaluable patients 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 (see section 5.2).

5.2 Pharmacokinetic properties

Absorption

Pomalidomide is absorbed with a maximum plasma concentration (C_{max}) occurring between 2 and 3 hours and is at least 73% absorbed following administration of single oral dose. The systemic exposure (AUC) of pomalidomide increases in an approximately linear and dose proportional manner. Following multiple doses, pomalidomide has an accumulation ratio of 27 to 31% on AUC.

Coadministration with a high-fat and high-calorie meal slows the rate of absorption, decreasing mean plasma C_{max} by approximately 27%, but has minimal effect on the overall extent of absorption with an 8% decrease in mean AUC. Therefore, pomalidomide can be administered without regard to food intake.

Distribution

Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours post-dose (approximately T_{max}) after 4 days of once daily dosing at 2 mg. In vitro binding of pomalidomide enantiomers to proteins in human plasma ranges from 12% to 44% and is not concentration dependent.

Biotransformation

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

The predominant metabolic pathways of excreted radioactivity are hydroxylation with subsequent glucuronidation, or hydrolysis. *In vitro*, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6. Pomalidomide is also a substrate of P-glycoprotein *in vitro*. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased mean exposure to pomalidomide by 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 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide to 50%. 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.

Based on *in vitro* data, pomalidomide is not an inhibitor or inducer of cytochrome P-450 isoenzymes, and does not inhibit any drug transporters that were studied. Clinically relevant interactions are not anticipated when pomalidomide is coadministered 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 approximately 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).

Population Pharmacokinetics (PK)

Based on population PK analysis using a two-compartment model, healthy subjects and MM patients had comparable apparent clearance (CL/F) and apparent central volume of distribution (V_2/F). In peripheral tissues, pomalidomide was preferentially taken up by tumours with apparent peripheral distribution clearance (Q/F) and apparent peripheral volume of distribution (V_3/F) 3.7-fold and 8-fold higher, respectively, than that of healthy subjects.

Paediatric population

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 half-life 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 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 body surface area (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.

Elderly

Based on population pharmacokinetic analyses in healthy subjects and multiple myeloma patients, no significant influence of age (19-83 years) on oral clearance of pomalidomide was observed. In clinical studies, no dose adjustment was required in elderly (> 65 years) patients exposed to pomalidomide (see section 4.2).

Renal impairment

Population pharmacokinetic analyses showed that the pomalidomide pharmacokinetic parameters were not remarkably affected in renally impaired patients (defined by creatinine clearance or estimated glomerular

filtration rate [eGFR]) compared to patients with normal renal function (CrCl ≥60 mL/minute). Mean normalised 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 ≤45 mL/minute/1.73 m^2) compared to patients with normal renal function. Mean normalised 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) compared to patients with normal renal function. Mean normalised AUC exposure to pomalidomide increased by 35.8% with a 90% CI [7.5% to 70.0%] in severe renal impairment patients requiring dialysis (CrCl <30mL/minute requiring dialysis) compared 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 requires dose adjustments.

Hepatic impairment

The pharmacokinetic parameters were modestly changed in hepatically impaired patients (defined by Child-Pugh criteria) compared to healthy subjects. Mean exposure to pomalidomide increased by 51% with a 90% confidence interval [9% to 110%] in mildly hepatically impaired patients compared to healthy subjects. Mean exposure to pomalidomide increased by 58% with a 90% confidence interval [13% to 119%] in moderately hepatically impaired patients compared to healthy subjects. Mean exposure to pomalidomide increased by 72% with a 90% confidence interval [24% to 138%] in severely hepatically impaired patients compared to healthy subjects. The mean increases in exposure to pomalidomide in each of these impairment groups are not of a magnitude for which adjustments in schedule or dose are required (see section 4.2).

5.3 Preclinical safety data

Repeat-dose toxicology studies

In rats, chronic administration of pomalidomide at doses of 50, 250, and 1000 mg/kg/day for 6 months was well tolerated. No adverse findings were noted up to 1000 mg/kg/day (175-fold exposure ratio relative to a 4 mg clinical dose).

In monkeys, pomalidomide was evaluated in repeat-dose studies of up to 9 months in duration. In these studies, monkeys exhibited greater sensitivity to pomalidomide effects than rats. The primary toxicities observed in monkeys were associated with the haematopoietic/lymphoreticular systems. In the 9-month study in monkeys with doses of 0.05, 0.1, and 1 mg/kg/day, morbidity and early euthanasia of 6 animals were observed at the dose of 1 mg/kg/day and were attributed to immunosuppressive effects (staphylococcal infection, decreased peripheral blood lymphocytes, chronic inflammation of the large intestine, histologic lymphoid depletion, and hypocellularity of bone marrow) at high exposures of pomalidomide (15-fold exposure ratio relative to a 4 mg clinical dose). These immunosuppressive effects resulted in early euthanasia of 4 monkeys due to poor health condition (watery stool, inappetence, reduced food intake, and weight loss); histopathologic evaluation of these animals showed chronic inflammation of the large intestine and villous atrophy of the small intestine. Staphylococcal infection was observed in 4 monkeys; 3 of these animals responded to antibiotic treatment and 1 died without treatment. In addition, findings consistent with acute myelogenous leukemia led to euthanasia of 1 monkey; clinical observations and clinical pathology and/or bone marrow alterations observed in this animal were consistent with immunosuppression.
Minimal or mild bile duct proliferation with associated increases in ALP and GGT were also observed at 1 mg/kg/day. Evaluation of recovery animals indicated that all treatment-related findings were reversible after 8 weeks of dosing cessation, except for proliferation of intrahepatic bile ducts observed in 1 animal in the 1 mg/kg/day group. The No Observed Adverse Effect Level (NOAEL) was 0.1 mg/kg/day (0.5-fold exposure ratio relative to a 4 mg clinical dose).

Genotoxicity/carcinogenicity

Pomalidomide was not mutagenic in bacterial and mammalian mutation assays, and did not induce chromosomal aberrations in human peripheral blood lymphocytes or micronuclei formation in polychromatic erythrocytes in bone marrow of rats administered doses up to 2000 mg/kg/day.
Carcinogenicity studies have not been conducted.

Fertility and early embryonic development
In a fertility and early embryonic development study in rats, pomalidomide was administered to males and females at doses of 25, 250, and 1000 mg/kg/day. Uterine examination on Gestation Day 13 showed a decrease in mean number of viable embryos and an increase in postimplantation loss at all dose levels. Therefore, the NOAEL for these observed effects was < 25 mg/kg/day (AUC_{24h} was 39960 ng•h/mL (nanogram•hour/millilitres) at this lowest dose tested, and the exposure ratio was 99-fold relative to a 4 mg clinical dose). When treated males on this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

Embryo-foetal development

Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. In the rat embryofoetal developmental toxicity study, malformations of absence of urinary bladder, absence of thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (central and/or neural arches) were observed at all dose levels (25, 250, and 1000 mg/kg/day).

There was no maternal toxicity observed in this study. Therefore, the maternal NOAEL was 1000 mg/kg/day, and the NOAEL for developmental toxicity was < 25 mg/kg/day (AUC_{24h} was 34340 ng•h/mL on Gestation Day 17 at this lowest dose tested, and the exposure ratio was 85-fold relative to a 4 mg clinical dose). In rabbits, pomalidomide at doses ranging from 10 to 250 mg/kg produced embryo-foetal developmental malformations. Increased cardiac anomalies were seen at all doses with significant increases at 250 mg/kg/day. At 100 and 250 mg/kg/day, there were slight increases in post-implantation loss and slight decreases in fetal body weights. At 250 mg/kg/day, fetal malformations included limb anomalies (flexed and/or rotated fore- and/or hindlimbs, unattached or absent digit) and associated skeletal malformations (not ossified metacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent tibia); moderate dilation of the lateral ventricle in the brain; abnormal placement of the right subclavian artery; absent intermediate lobe in the lungs; low-set kidney; altered liver morphology; incompletely or not ossified pelvis; an increased average for supernumerary thoracic ribs and a reduced average for ossified tarsals. Slight reduction in maternal body weight gain, significant reduction in triglycerides, and significant decrease in absolute and relative spleen weights were observed at 100 and 250 mg/kg/day. The maternal NOAEL was 10 mg/kg/day, and the developmental NOAEL was <10 mg/kg/day (AUC_{24h} was 418 ng•h/mL on Gestation Day 19 at this lowest dose tested, which was similar to that obtained from a 4 mg clinical dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Cellulose, microcrystalline (E460)
Maltodextrin
Sodium stearyl fumarate

Capsule body

[product name] 1 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)

[product name] 2 mg hard capsules
Gelatin

Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

[product name] 3 mg hard capsules
Gelatin
Titanium dioxide (E171)
Indigo carmine aluminium lake (E132)

[product name] 4 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)
Erythrosine (E127)

Capsule cap

[product name] 1 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

[product name] 2 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

[product name] 3 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

[product name] 4 mg hard capsules
Gelatin
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)

Printing ink

Shellac glaze ~45% (20% esterified)
Titanium dioxide (E171)
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The capsules are packaged in oPA/Aluminium/PVC/Aluminium blisters.

Pack size of 14, 21, 14x1 or 21x1 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Capsules should not be opened or crushed. If powder from pomalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If pomalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.

Healthcare professionals and caregivers should wear disposable gloves when handling the blister or capsule. Gloves should then be removed carefully to prevent skin exposure, placed in a sealable plastic polyethylene bag and disposed of in accordance with local requirements. Hands should then be washed thoroughly with soap and water. Women who are pregnant or suspect they may be pregnant should not handle the blister or capsule (see section 4.4).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Unused medicinal product should be returned to the pharmacist at the end of treatment.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Innovis Pharma S.A.
Marathonos Avenue 144
15351 Pallini Attica
Griekenland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 132108
RVG 132110
RVG 132111
RVG 132113

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 28 juni 2024

10. DATUM VAN HERZIENING VAN DE TEKST