

POMALIDOMIDE MALAYSIA ALL LEAFLET

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Glue Point

POMAGEN HARD CAPSULES
1mg, 2mg, 3mg, 4mg
pomalidomide

POMAGEN HEADER
HARD CAPSULES
1mg, 2mg, 3mg, 4mg
pomalidomide

2D Pharma Code Scan Path
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Glue Point

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Controlled Medicine

POMAGEN HARD CAPSULES 1mg, 2mg, 3mg, 4mg pomalidomide



1. NAME OF THE MEDICINAL PRODUCT

Pomagen Hard Capsules 1 mg
Pomagen Hard Capsules 2 mg
Pomagen Hard Capsules 3 mg
Pomagen Hard Capsules 4 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 1 mg of pomalidomide, the sodium content is 0.04 mg
Each hard capsule contains 2 mg of pomalidomide, the sodium content is 0.08 mg
Each hard capsule contains 3 mg of pomalidomide, the sodium content is 0.11 mg
Each hard capsule contains 4 mg of pomalidomide, the sodium content is 0.15 mg
For excipients, see *List of Excipients*

3. PHARMACEUTICAL FORM

Hard capsule.
Pomagen Hard Capsules 1 mg
Yellow opaque cap and yellow opaque body, capsule shell size No. 4 imprinted in black ink with "LP" on the cap and "664" on the body and containing yellow granular powder
Pomagen Hard Capsules 2 mg
Orange opaque cap and Orange opaque body, capsule shell size No. 3 imprinted in black ink with "LP" on the cap and "665" on the body and containing yellow granular powder
Pomagen Hard Capsules 3 mg
Light green opaque cap and Light green opaque body, capsule shell size No. 2 imprinted in black ink with "LP" on the cap and "690" on the body and containing yellow granular powder
Pomagen Hard Capsules 4 mg
Blue opaque cap and Blue opaque body, capsule shell size No. 2 imprinted in black ink with "LP" on the cap and "667" on the body and containing yellow granular powder

4. CLINICAL PARTICULARS

4.1 Indications

POMAGEN in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior treatment regimen including lenalidomide.
POMAGEN 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 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.

Posology

• Pomalidomide in combination with bortezomib and dexamethasone

The recommended starting dose of POMAGEN is 4 mg 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/m² intravenous or subcutaneous once daily, on the days shown in Table 1. The recommended dose of dexamethasone is 20 mg 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 POMAGEN 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 $\geq 1 \times 10^9/L$ and the platelet count must be $\geq 50 \times 10^9/L$.
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** $<0.5 \times 10^9/L$ or Febrile neutropenia (fever $\geq 38.5^\circ C$ and ANC $<1 \times 10^9/L$)	Interrupt pomalidomide treatment for remainder of cycle. Follow CBC*** weekly.
ANC return to $\geq 1 \times 10^9/L$	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop $<0.5 \times 10^9/L$	Interrupt pomalidomide treatment.
ANC return to $\geq 1 \times 10^9/L$	Resume pomalidomide treatment at one dose level lower than the previous dose.
Thrombocytopenia Platelet count $<25 \times 10^9/L$	Interrupt pomalidomide treatment for remainder of cycle. Follow CBC*** weekly.
Platelet count return to $\geq 50 \times 10^9/L$	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop $<25 \times 10^9/L$	Interrupt pomalidomide treatment.
Platelet count return to $\geq 50 \times 10^9/L$	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.
Other Other $\geq$ 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 $\leq$ 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 medicinal product should be discontinued.

Strong CYP1A2 inhibitors

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

Bortezomib dose modification or interruption

For instructions on dose interruptions or reductions for bortezomib related adverse reactions, physicians should refer to bortezomib Package Insert.

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 Package Insert.

Table 4. Dexamethasone dose modification instructions

Toxicity	Dose modification
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia $\geq$ Grade 3	Interrupt dose until symptoms are controlled. Add H2 blocker or equivalent and resume at one dose level lower than previous dose.
Oedema $\geq$ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration $\geq$ Grade 2	Interrupt dose until symptoms resolve. Resume at one dose level lower than previous dose.
Muscle weakness $\geq$ Grade 2	Interrupt dose until muscle weakness $\leq$ Grade 1. Resume at one dose level lower than previous dose.
Hyperglycaemia $\geq$ 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 $\geq$ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until the adverse event resolves to $\leq$ 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 POMAGEN is 4 mg orally once daily on Days 1 to 21 of each 28-day cycle.
The recommended dose of dexamethasone is 40 mg 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 Package Insert.

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

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.

Hepatic impairment

Patients with serum total bilirubin $> 1.5 \times$ ULN (upper limit of normal range) were excluded from clinical studies. Hepatic impairment has a modest effect on the pharmacokinetics of pomalidomide. 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.

Paediatric population

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. There is no relevant use of POMAGEN in children aged 0-17 years for the indication of multiple myeloma.

Administration

Oral use

POMAGEN should be taken orally at the same time each day. The capsules should not be opened, broken or chewed. This medicinal product should be swallowed whole, preferably with water, with or without food. If the patient forgets to take a dose of POMAGEN 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
- Male patients unable to follow or comply with the required contraceptive measures
- Hypersensitivity to the active substance or to any of the excipients in POMAGEN

4.4 Warnings and Precautions

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.
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*
 - 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 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 sterilization
 - 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 at least 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 sterilization
- 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. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with

dexamethasone.

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.

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to pomalidomide, the Marketing Authorization 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. 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. Complete blood counts should be monitored 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 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). 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 $\geq$ 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, 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. Physicians should carefully evaluate

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 Pregnancy, Lactation and Fertility
Women of childbearing potential / Contraception in males and females
Women of childbearing potential should use at least one 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 at least 7 days after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

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.

Breast-feeding
It is not known if 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 nursing infants from pomalidomide, a decision must be made whether to discontinue nursing 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 mother.

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

4.7 Effects on ability to drive and use machines
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 Side Effects
Summary of the safety profile
▪ *Pomalidomide in combination with bortezomib and dexamethasone*
The most commonly reported blood and lymphatic system disorders were neutropenia, thrombocytopenia and anaemia. Other most frequently reported adverse reactions included peripheral sensory neuropathy, fatigue, diarrhoea, constipation, and oedema peripheral. The most commonly reported Grade 3 or 4 adverse reactions were blood and lymphatic system disorders including neutropenia, thrombocytopenia and anaemia. The most commonly reported serious adverse reaction was pneumonia. Other serious adverse reactions reported included pyrexia, lower respiratory tract infection, influenza, pulmonary embolism, atrial fibrillation, and acute kidney injury.

▪ *Pomalidomide in combination with dexamethasone*
The most commonly reported adverse reactions have been blood and lymphatic system disorders including anaemia, neutropenia and thrombocytopenia; in general disorders and administration site conditions including fatigue, pyrexia and oedema peripheral; and in infections and infestations including pneumonia. Peripheral neuropathy adverse reactions were reported and venous embolic or thrombotic (VTE) adverse reactions were reported. The most commonly reported Grade 3 or 4 adverse reactions were in the blood and lymphatic system disorders including neutropenia, anaemia and thrombocytopenia; in infections and infestations including pneumonia; and in general disorders and administration site conditions including fatigue, pyrexia and oedema peripheral. The most commonly reported serious adverse reaction was pneumonia. Other serious adverse reactions reported included febrile neutropenia, neutropenia, thrombocytopenia and VTE adverse reactions. 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), uncommon (≥1/1000 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	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
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
<i>Clostridium difficile</i> 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 (include 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	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	-	-
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	Common
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	-	-	-
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. If pomalidomide is taken during pregnancy, a teratogenic effect of pomalidomide in humans is expected.

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 any 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. 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) patients. 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) patients 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. 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 randomization 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.

▪ *Pomalidomide in combination with dexamethasone*
Patients with ongoing peripheral neuropathy ≥Grade 2 were excluded from clinical studies. Peripheral neuropathy occurred in 12.3% 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.

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.

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.

4.9 Overdose
Pomalidomide doses as high as 50 mg as a single dose in healthy volunteers, and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse reactions related to overdose. In studies, pomalidomide was found to be removed by haemodialysis. In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamics properties
Pharmacotherapeutic group: Immunomodulating agent, 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 deoxyubiquitinase 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, substrate proteins Aiolos and Ikaros are targeted for ubiquitination and subsequent degradation leading to direct cytotoxic and immunomodulatory effects. Pomalidomide therapy led to reduction in the levels of Ikaros in patients with relapsed lenalidomide-refractory multiple myeloma.

5.2 Pharmacokinetic properties
Absorption
Pomalidomide is absorbed with a 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.

Co-administration 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. 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 healthy subjects who received a single oral dose of [14C]-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. 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. 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. 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 data, pomalidomide is not an inhibitor or inducer of cytochrome P-450 isoenzymes, and does not inhibit any drug transporters that were evaluated. Clinically relevant drug-drug interactions are not anticipated when pomalidomide is co-administered with substrates of these pathways.

Elimination
Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy patients 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 [14C]-pomalidomide (2 mg) to healthy patients, 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, healthy patients and MM patients had comparable apparent clearance (CL/F) and apparent central volume of distribution (V2/F). In peripheral tissues, pomalidomide was preferentially taken up by tumors with apparent peripheral distribution clearance (Q/F) and apparent peripheral volume of distribution (V3/F) 3.7-fold and 8-fold higher, respectively, than that of healthy patients.

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/m² dose levels, respectively. AUC₀₋₂₄ 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/m²/day to 3.4 mg/m²/day were determined in patients ages from 4 to 20 years with 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 patients and multiple myeloma patients, no significant influence of age (19-83 years) on oral clearance of pomalidomide was observed. In clinical studies, no dosage adjustment was required in elderly (>65 years) patients exposed to pomalidomide.

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 normalized AUC exposure to pomalidomide was 98.2% in moderate renal impairment patients (eGFR ≥30 to <45 mL/minute/1.73 m²) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m²) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide increased by 35.8% in severe renal impairment patients requiring dialysis (CrCl <30 mL/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 require dosage adjustments.

Hepatic impairment
The pharmacokinetic parameters were modestly changed in hepatically impaired patients (defined by Child-Pugh criteria) compared to healthy patients. Mean exposure to pomalidomide increased by 51% in mildly hepatically impaired patients compared to healthy patients. Mean exposure to pomalidomide increased by 58% in moderately hepatically impaired patients compared to healthy patients. Mean exposure to pomalidomide increased by 72% in severely hepatically impaired patients compared to healthy patients. 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsule content
Isomalt 801, Isomalt 721, Pregelatinized starch, Sodium stearyl fumar