ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 1 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 1 mg of pomalidomide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Imnovid 1 mg hard capsule: Dark blue opaque cap and yellow opaque body, imprinted "POML" in white ink and "1 mg" in black ink, size 4, hard gelatin capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imnovid 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.

Posology
The recommended starting dose of Imnovid is 4 mg once daily taken orally on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

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

Treatment should be discontinued upon progression of disease.

Pomalidomide dose modification or interruption
Instructions for dose interruptions and reductions for pomalidomide related to haematologic adverse reactions are outlined in the table below:

- *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, follow CBC** weekly.
• ANC return to ≥1 x 10^9/l	Resume pomalidomide treatment at 3 mg daily.
• 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 1 mg less than the previous dose.
Thrombocytopenia • Platelet count <25 x 10^9/l	Interrupt pomalidomide treatment, follow CBC** weekly
• Platelet count return to ≥50 x 10^9/l	Resume pomalidomide treatment at 3 mg daily
• 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 1 mg less than the previous dose

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

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.

In case of neutropaenia, the physician should consider the use of growth factors.

For other Grade 3 or 4 adverse reactions judged to be related to pomalidomide, stop treatment and restart treatment at 1 mg less than the previous dose when an adverse reaction has resolved to ≤ Grade 2 at the physician's discretion.

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

Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, 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, and should not be resumed following discontinuation from these reactions.

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

- *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 decrease one dose level when dose restarted.
Oedema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Restart with dose decreased by one level.
Hyperglycaemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed
Acute pancreatitis	Discontinue patient from dexamethasone treatment regimen.
Other ≥ Grade 3dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤ Grade 2. Resume with dose reduced by one level.

Dexamethasone dose reduction levels:
Dose reduction levels (≤ 75 years of age): Starting dose 40 mg; dose level -1 20 mg; dose level-2 10 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Dose reduction levels (> 75 years of age): Starting dose 20 mg; dose level -1 12 mg; dose level-2 8 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

Special populations

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

Older people
No dose adjustment is required for pomalidomide. For patients >75 years of age, the starting dose of dexamethasone is 20 mg once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

Renal impairment
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 > 2.0 mg/dL 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.

Method of administration
Oral use.
Imnovid should be taken at the same time each day. The capsules should not be opened, broken or chewed (see section 6.6). This medicinal product should be swallowed whole, preferably with water, with or without food. If the patient forgets to take a dose of Imnovid 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*
- 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, 4 weeks before starting treatment, throughout the entire duration of treatment, and 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 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. As a precaution, 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, during treatment and for 7 days after dose interruptions and/or cessation of treatment. Vasectomised males 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.

<u>Contraception</u>
Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 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 method 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 every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men

Pomalidomide is present in human semen during treatment. As a precaution, and taking into account special populations with potentially prolonged elimination time such as renal impairment, all male patients taking pomalidomide, including those who have had a vasectomy, 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.
Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for 7 days following discontinuation of pomalidomide.

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 7 days following discontinuation of pomalidomide.

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 therapy 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 in accordance with the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and /or dispensing controls, and the collection of detailed data 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 4 weeks, 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 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.

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 failure events, including congestive cardiac failure and pulmonary oedema (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 failure.

Tumour lysis syndrome
Tumour lysis syndrome may occur.The patients at greatest risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Second Primary Malignancies
Second primary malignancies, such as non-melanoma skin cancer, have been reported in patients receiving 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 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Imnovid on other medicinal products
Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug 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 drug-drug 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 Imnovid
Pomalidomide is partly metabolised by CYP1A2 and CYP3A4/5. It is also a substrate for P-glycoprotein. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased 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 section 4.3 and section 4.4.

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 should be made whether to discontinue nursing or to discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

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

4.7 Effects on ability to drive and use machines

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

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

The frequencies of adverse reactions are those reported in the pomalidomide plus dexamethasone arm of study CC-4047-MM-003 (n = 302) and from post marketing data. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined in accordance with current guidance, as: very common (≥1/10), common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100).

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

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Metabolism and nutrition disorders	**Very Common** Decreased appetite **Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Tumour lysis syndrome*	**Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Decreased appetite Tumour lysis syndrome*
Psychiatric disorders	**Common** Confusional state	**Common** Confusional state
Nervous system disorders	**Common** Depressed level of consciousness Peripheral sensory neuropathy Dizziness Tremor Intracranial haemorrhage* **Uncommon** Cerebrovascular accident*	**Common** Depressed level of consciousness **Uncommon** Peripheral sensory neuropathy Dizziness Tremor Cerebrovascular accident* Intracranial haemorrhage*
Ear and labyrinth disorders	**Common** Vertigo	**Common** Vertigo
Vascular disorders	**Common** Deep vein thrombosis	**Uncommon** Deep vein thrombosis
Cardiac disorders	**Common** Cardiac failure* Atrial fibrillation* Myocardial infarction*	**Common** Cardiac failure* Atrial fibrillation* **Uncommon** Myocardial infarction*
Immune system disorders	**Common** Angioedema* Urticaria*	**Uncommon** Angioedema* Urticaria*

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea Cough **Common** Pulmonary embolism Epistaxis* Interstitial lung disease*	**Common** Dyspnoea **Uncommon** Pulmonary embolism Cough Epistaxis* Interstitial lung disease*
Gastrointestinal disorders	**Very Common** Diarrhoea Nausea Constipation **Common** Vomiting Gastrointestinal haemorrhage	**Common** Diarrhoea Vomiting Constipation **Uncommon** Nausea Gastrointestinal haemorrhage
Hepatobiliary disorders	**Uncommon** Hyperbilirubinaemia Hepatitis*	**Uncommon** Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	**Common** Rash Pruritus **Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms* Toxic Epidermal Necrolysis* Stevens-Johnson Syndrome*	**Common** Rash **Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms* Toxic Epidermal Necrolysis* Stevens-Johnson Syndrome*
Musculoskeletal and connective tissue disorders	**Very Common** Bone pain Muscle spasms	**Common** Bone pain **Uncommon** Muscle spasms

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Renal and urinary disorders	**Common** Renal failure Urinary retention	**Common** Renal failure **Uncommon** Urinary retention
Reproductive system and breast disorders	**Common** Pelvic pain	**Common** Pelvic pain
General disorders and administration site conditions	**Very Common** Fatigue Pyrexia Oedema peripheral	**Common** Fatigue Pyrexia Oedema peripheral
Investigations	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased Blood uric acid increased*	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased **Uncommon** Blood uric acid increased*

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

Description of selected adverse reactions

Teratogenicity
Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis (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 45.3% of patients who received pomalidomide plus low dose dexamethasone (Pom + LD-Dex), and in 19.5% of patients who received high dose dexamethasone (HD-Dex). Neutropenia was Grade 3 or 4 in 41.7% of patients who received Pom + LD-Dex, compared with 14.8% who received HD-Dex. In Pom + LD-Dex treated patients neutropenia was infrequently serious (2.0% of patients), did not lead to treatment discontinuation, and was associated with treatment interruption in 21.0% of patients, and with dose reduction in 7.7% of patients.

Febrile neutropenia (FN) was experienced in 6.7% of patients who received Pom + LD-Dex, and in no patients who received HD-Dex. All were reported to be Grade 3 or 4. FN was reported to be serious in

4.0% of patients. FN was associated with dose interruption in 3.7% of patients, and with dose reduction in 1.3% of patients, and with no treatment discontinuations.

Thrombocytopenia occurred in 27.0% of patients who received Pom + LD-Dex, and 26.8% of patients who received HD-Dex. Thrombocytopenia was Grade 3 or 4 in 20.7% of patients who received Pom + LD-Dex and in 24.2% who received HD-Dex. In Pom + LD-Dex treated patients, thrombocytopenia was serious in 1.7% of patients, led to dose reduction in 6.3% of patients, to dose interruption in 8% of patients and to treatment discontinuation in 0.7% of patients. (see sections 4.2 and 4.4)

Infection
Infection was the most common non haematological toxicity; it occurred in 55.0% of patients who received Pom + LD-Dex, and 48.3% of patients who received HD-Dex. Approximately half of those infections were Grade 3 or 4; 24.0% in Pom + LD-Dex-treated patients and 22.8% in patients who received HD-Dex.

In Pom + LD-Dex treated patients pneumonia and upper respiratory tract infections were the most commonly reported infections (in 10.7% and 9.3% of patients, respectively);with 24.3% of reported infections being serious and fatal infections (Grade 5) occurring in 2.7% of treated patients. In Pom + LD-Dex treated patients infections led to dose discontinuation in 2.0% of patients, to treatment interruption in 14.3% of patients, and to a dose reduction in 1.3% of patients.

Thromboembolic events
Venous embolic or thrombotic events (VTE) occurred in 3.3% of patients who received Pom + LD-Dex, and 2.0% of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1.3 % of patients who received Pom + LD-Dex, and no patients who received HD-Dex. In Pom + LD-Dex treated patients, VTE was reported as serious in 1.7% of patients, no fatal reactions were reported in clinical studies, and VTE was not associated with dose discontinuation.

Prophylaxis with 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).

Peripheral neuropathy
Patients with ongoing peripheral neuropathy ≥Grade 2 were excluded from clinical studies. Peripheral neuropathy, mostly Grade 1 or 2 occurred in 12.3% patients who received Pom + LD-Dex, and 10.7% of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1.0 % of patients who received Pom + LD-Dex and in 1.3% of patients who received HD-Dex. In patients treated with Pom + LD-Dex, no peripheral neuropathy reactions were reported to have been serious in clinical trials and peripheral neuropathy led to dose discontinuation in 0.3% of patients (see section 4.4).

Median time to onset of neuropathy was 2.1 weeks, varying from 0.1 to 48.3 weeks. Median time to onset was earlier in patients who received HD-Dex compared with Pom + LD-Dex (1.3 weeks versus 2.1 weeks).

Median time to resolution was 22.4 weeks in patients who received Pom + LD-Dex and 13.6 weeks in patients who received HD-Dex. The lower limit of the 95% CI was 5.3 week in the Pom +LD-Dex-treated patients and 2.0 weeks in patients who received HD-Dex.

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 and severe cutaneous reactions including SJS, TEN and DRESS has 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).

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, and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse events related to overdose. Pomalidomide was removed by haemodialysis.

In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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.

Clinical efficacy and safety
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 (PFS) by International Myeloma Working Group (IMWG criteria). For the 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%).

Progression-free survival 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.

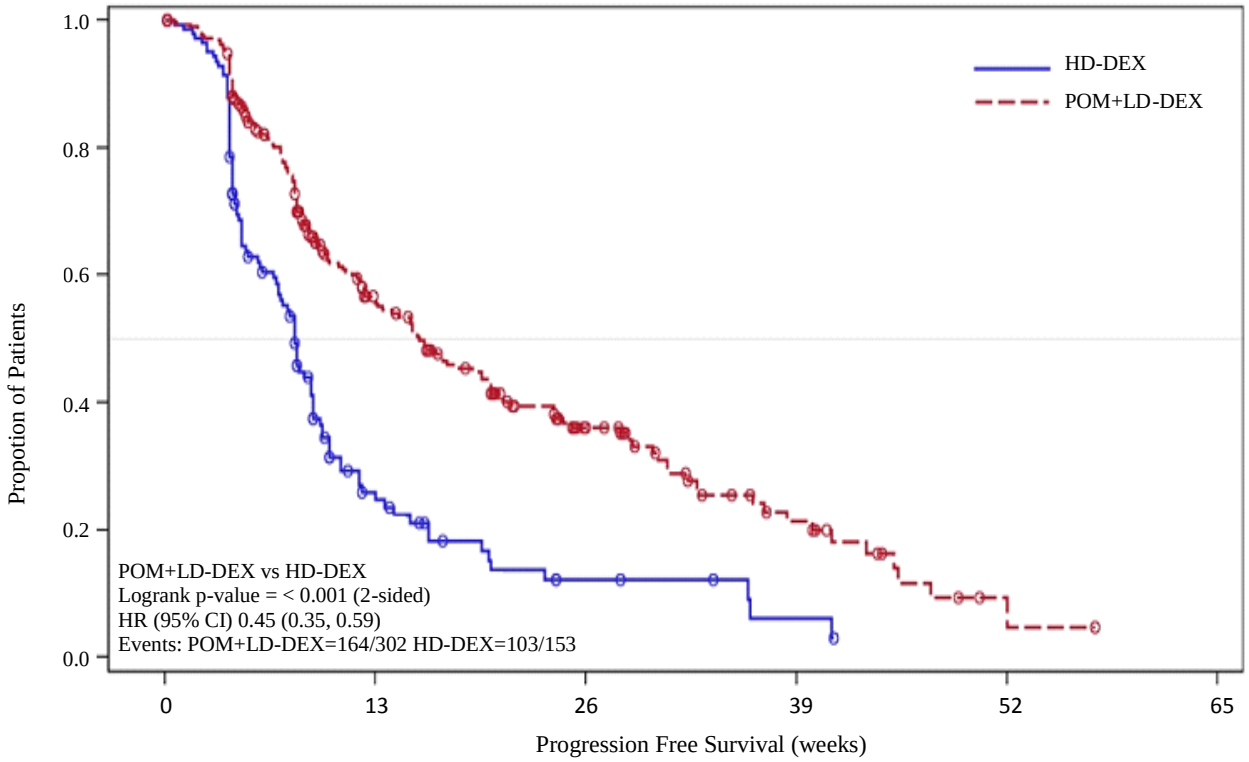
Progression Free Survival is summarised in Table 1 for the ITT population. Kaplan-Meier curve for PFS for the ITT population is provided in Figure 1.

Table 1: 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 drugs), 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 1: 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 2 for the ITT population. Kaplan-Meier curve for OS for the ITT population is provided in Figure 2.

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.

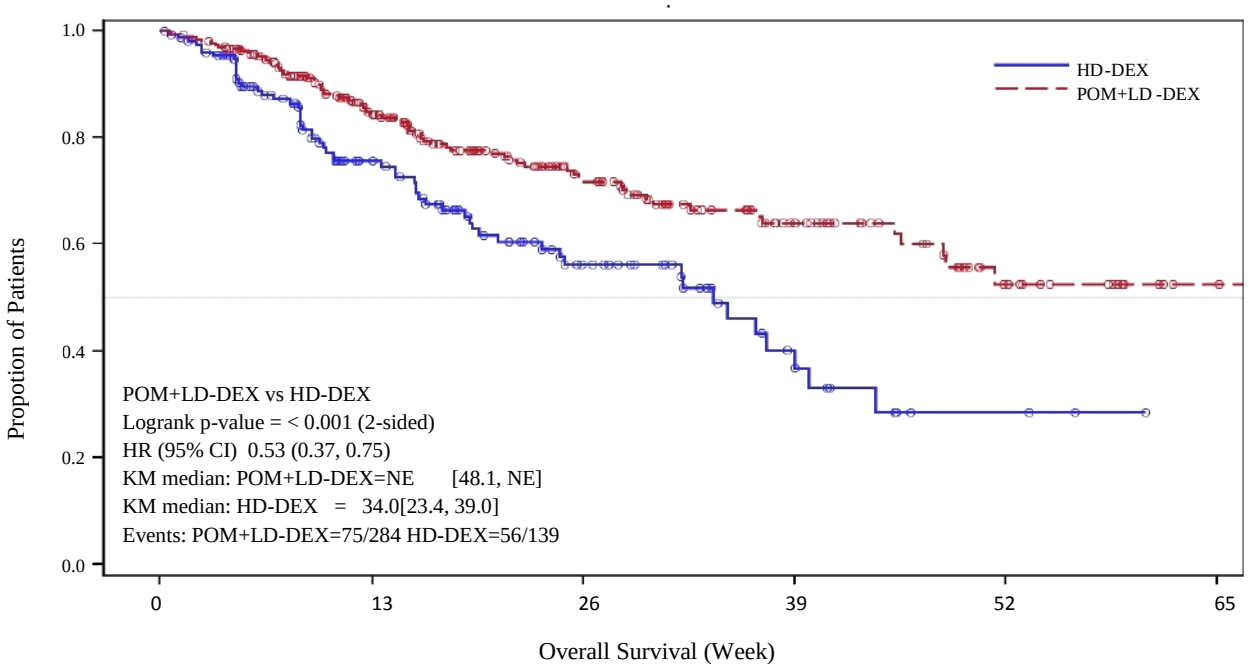
Table 2: Overall Survival: ITT Population

	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)

	Statistics	Pom+LD-Dex (N=302)	HD-Dex (N=153)
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]	
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 2: Kaplan-Meier Curve of Overall Survival (ITT Population)



cutoff: 07 Sep 2012

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Imnovid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

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 drug-drug 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

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 tumors 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

No data are available on administration of pomalidomide to paediatric or adolescent patients (< 18 years of age).

Older people

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 dosage adjustment was required in elderly (> 65 years) patients exposed to pomalidomide. Please 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 normalized AUC exposure to pomalidomide was 98.2% with a 90% confidence interval [77.4% to 120.6%] in moderate renal impairment patients (eGFR ≥30 to ≤45mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% with a 90% confidence interval [79.7% to 127.0%] in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized 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 require dosage 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 dosages 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 dosage 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 dosage 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 dosages ranging from 10 to 250 mg/kg produced embryo-foetal developmental malforma tions. 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 content:
Mannitol
Pregelatinised starch
Sodium stearyl fumarate

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

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 Polyvinyl chloride (PVC)/ polychlorotrifluoroethylene (PCTFE) blisters with push through aluminium foil.

Pack size of 21 capsules.

6.6 Special precautions for disposal and other handling

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

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. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/850/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 2 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 2 mg of pomalidomide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Imnovid 2 mg hard capsule: Dark blue opaque cap and orange opaque body, imprinted “POML 2 mg” in white ink, size 2, hard gelatin capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imnovid 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.

Posology
The recommended starting dose of Imnovid is 4 mg once daily taken orally on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

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

Treatment should be discontinued upon progression of disease.

Pomalidomide dose modification or interruption
Instructions for dose interruptions and reductions for pomalidomide related to haematologic adverse reactions are outlined in the table below:

- *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, follow CBC** weekly.
• ANC return to ≥1 x 10^9/l	Resume pomalidomide treatment at 3 mg daily.
• 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 1 mg less than the previous dose.
Thrombocytopenia • Platelet count <25 x 10^9/l	Interrupt pomalidomide treatment, follow CBC** weekly
• Platelet count return to ≥50 x 10^9/l	Resume pomalidomide treatment at 3 mg daily
• 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 1 mg less than the previous dose

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

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.

In case of neutropaenia, the physician should consider the use of growth factors.

For other Grade 3 or 4 adverse reactions judged to be related to pomalidomide, stop treatment and restart treatment at 1 mg less than the previous dose when an adverse reaction has resolved to ≤ Grade 2 at the physician's discretion.

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

Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, 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, and should not be resumed following discontinuation from these reactions.

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

- *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 decrease one dose level when dose restarted.
Oedema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Restart with dose decreased by one level.
Hyperglycaemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed
Acute pancreatitis	Discontinue patient from dexamethasone treatment regimen.
Other ≥ Grade 3dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤ Grade 2. Resume with dose reduced by one level.

Dexamethasone dose reduction levels:
Dose reduction levels (≤ 75 years of age): Starting dose 40 mg; dose level -1 20 mg; dose level-2 10 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Dose reduction levels (> 75 years of age): Starting dose 20 mg; dose level -1 12 mg; dose level-2 8 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

Special populations

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

Older people
No dose adjustment is required for pomalidomide. For patients >75 years of age, the starting dose of dexamethasone is 20 mg once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

Renal impairment
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 > 2.0 mg/dL 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.

Method of administration
Oral use.
Imnovid should be taken at the same time each day. The capsules should not be opened, broken or chewed (see section 6.6). This medicinal product should be swallowed whole, preferably with water, with

or without food. If the patient forgets to take a dose of Imnovid 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*
- 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, 4 weeks before starting treatment, throughout the entire duration of treatment, and 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 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. As a precaution, 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, during treatment and for 7 days after dose interruptions and/or cessation of treatment. Vasectomised males 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 one effective method of contraception for 4 weeks before therapy, during therapy, and until 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 method 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 every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men

Pomalidomide is present in human semen during treatment. As a precaution, and taking into account special populations with potentially prolonged elimination time such as renal impairment, all male patients taking pomalidomide, including those who have had a vasectomy, 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.
Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for 7 days following discontinuation of pomalidomide.

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 7 days following discontinuation of pomalidomide.

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 therapy 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 in accordance with the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for

prescribing and /or dispensing controls, and the collection of detailed data 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 4 weeks, 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 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.

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 failure events, including congestive cardiac failure and pulmonary oedema (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 failure.

Tumour lysis syndrome
Tumour lysis syndrome may occur.The patients at greatest risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Second Primary Malignancies
Second primary malignancies, such as non-melanoma skin cancer, have been reported in patients receiving 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 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Imnovid on other medicinal products
Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug 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 drug-drug 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 Imnovid
Pomalidomide is partly metabolised by CYP1A2 and CYP3A4/5. It is also a substrate for P-glycoprotein. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased 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 section 4.3 and section 4.4.

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 should be made whether to discontinue nursing or to

discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

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

4.7 Effects on ability to drive and use machines

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

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

The frequencies of adverse reactions are those reported in the pomalidomide plus dexamethasone arm of study CC-4047-MM-003 (n = 302) and from post marketing data. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined in accordance with current guidance, as: very common (≥1/10), common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100).

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

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Metabolism and nutrition disorders	**Very Common** Decreased appetite **Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Tumour lysis syndrome*	**Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Decreased appetite Tumour lysis syndrome*
Psychiatric disorders	**Common** Confusional state	**Common** Confusional state
Nervous system disorders	**Common** Depressed level of consciousness Peripheral sensory neuropathy Dizziness Tremor Intracranial haemorrhage* **Uncommon** Cerebrovascular accident*	**Common** Depressed level of consciousness **Uncommon** Peripheral sensory neuropathy Dizziness Tremor Cerebrovascular accident* Intracranial haemorrhage*
Ear and labyrinth disorders	**Common** Vertigo	**Common** Vertigo
Vascular disorders	**Common** Deep vein thrombosis	**Uncommon** Deep vein thrombosis
Cardiac disorders	**Common** Cardiac failure* Atrial fibrillation* Myocardial infarction*	**Common** Cardiac failure* Atrial fibrillation* **Uncommon** Myocardial infarction*
Immune system disorders	**Common** Angioedema* Urticaria*	**Uncommon** Angioedema* Urticaria*

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea Cough **Common** Pulmonary embolism Epistaxis* Interstitial lung disease*	**Common** Dyspnoea **Uncommon** Pulmonary embolism Cough Epistaxis* Interstitial lung disease*
Gastrointestinal disorders	**Very Common** Diarrhoea Nausea Constipation **Common** Vomiting Gastrointestinal haemorrhage	**Common** Diarrhoea Vomiting Constipation **Uncommon** Nausea Gastrointestinal haemorrhage
Hepatobiliary disorders	**Uncommon** Hyperbilirubinaemia Hepatitis*	**Uncommon** Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	**Common** Rash Pruritus **Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms* Toxic Epidermal Necrolysis* Stevens-Johnson Syndrome*	**Common** Rash **Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms* Toxic Epidermal Necrolysis* Stevens-Johnson Syndrome*
Musculoskeletal and connective tissue disorders	**Very Common** Bone pain Muscle spasms	**Common** Bone pain **Uncommon** Muscle spasms

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Renal and urinary disorders	**Common** Renal failure Urinary retention	**Common** Renal failure **Uncommon** Urinary retention
Reproductive system and breast disorders	**Common** Pelvic pain	**Common** Pelvic pain
General disorders and administration site conditions	**Very Common** Fatigue Pyrexia Oedema peripheral	**Common** Fatigue Pyrexia Oedema peripheral
Investigations	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased Blood uric acid increased*	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased **Uncommon** Blood uric acid increased*

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

Description of selected adverse reactions

Teratogenicity
Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis (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 45.3% of patients who received pomalidomide plus low dose dexamethasone (Pom + LD-Dex), and in 19.5% of patients who received high dose dexamethasone (HD-Dex). Neutropenia was Grade 3 or 4 in 41.7% of patients who received Pom + LD-Dex, compared with 14.8% who received HD-Dex. In Pom + LD-Dex treated patients neutropenia was infrequently serious (2.0% of patients), did not lead to treatment discontinuation, and was associated with treatment interruption in 21.0% of patients, and with dose reduction in 7.7% of patients.

Febrile neutropenia (FN) was experienced in 6.7% of patients who received Pom + LD-Dex, and in no patients who received HD-Dex. All were reported to be Grade 3 or 4. FN was reported to be serious in

4.0% of patients. FN was associated with dose interruption in 3.7% of patients, and with dose reduction in 1.3% of patients, and with no treatment discontinuations.

Thrombocytopenia occurred in 27.0% of patients who received Pom + LD-Dex, and 26.8% of patients who received HD-Dex. Thrombocytopenia was Grade 3 or 4 in 20.7% of patients who received Pom + LD-Dex and in 24.2% who received HD-Dex. In Pom + LD-Dex treated patients, thrombocytopenia was serious in 1.7% of patients, led to dose reduction in 6.3% of patients, to dose interruption in 8% of patients and to treatment discontinuation in 0.7% of patients. (see sections 4.2 and 4.4)

Infection
Infection was the most common non haematological toxicity; it occurred in 55.0% of patients who received Pom + LD-Dex, and 48.3% of patients who received HD-Dex. Approximately half of those infections were Grade 3 or 4; 24.0% in Pom + LD-Dex-treated patients and 22.8% in patients who received HD-Dex.

In Pom + LD-Dex treated patients pneumonia and upper respiratory tract infections were the most commonly reported infections (in 10.7% and 9.3% of patients, respectively); with 24.3% of reported infections being serious and fatal infections (Grade 5) occurring in 2.7% of treated patients. In Pom + LD-Dex treated patients infections led to dose discontinuation in 2.0% of patients, to treatment interruption in 14.3% of patients, and to a dose reduction in 1.3% of patients.

Thromboembolic events
Venous embolic or thrombotic events (VTE) occurred in 3.3% of patients who received Pom + LD-Dex, and 2.0% of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1.3 % of patients who received Pom + LD-Dex, and no patients who received HD-Dex. In Pom + LD-Dex treated patients, VTE was reported as serious in 1.7% of patients, no fatal reactions were reported in clinical studies, and VTE was not associated with dose discontinuation.

Prophylaxis with 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).

Peripheral neuropathy
Patients with ongoing peripheral neuropathy ≥Grade 2 were excluded from clinical studies. Peripheral neuropathy, mostly Grade 1 or 2 occurred in 12.3% patients who received Pom + LD-Dex, and 10.7% of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1.0 % of patients who received Pom + LD-Dex and in 1.3% of patients who received HD-Dex. In patients treated with Pom + LD-Dex, no peripheral neuropathy reactions were reported to have been serious in clinical trials and peripheral neuropathy led to dose discontinuation in 0.3% of patients (see section 4.4).

Median time to onset of neuropathy was 2.1 weeks, varying from 0.1 to 48.3 weeks. Median time to onset was earlier in patients who received HD-Dex compared with Pom + LD-Dex (1.3 weeks versus 2.1 weeks).

Median time to resolution was 22.4 weeks in patients who received Pom + LD-Dex and 13.6 weeks in patients who received HD-Dex. The lower limit of the 95% CI was 5.3 week in the Pom +LD-Dex-treated patients and 2.0 weeks in patients who received HD-Dex.

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 and severe cutaneous reactions including SJS, TEN and DRESS has 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).

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, and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse events related to overdose. Pomalidomide was removed by haemodialysis.

In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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.

Clinical efficacy and safety
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 (PFS) by International Myeloma Working Group (IMWG criteria). For the 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%).

Progression-free survival 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.

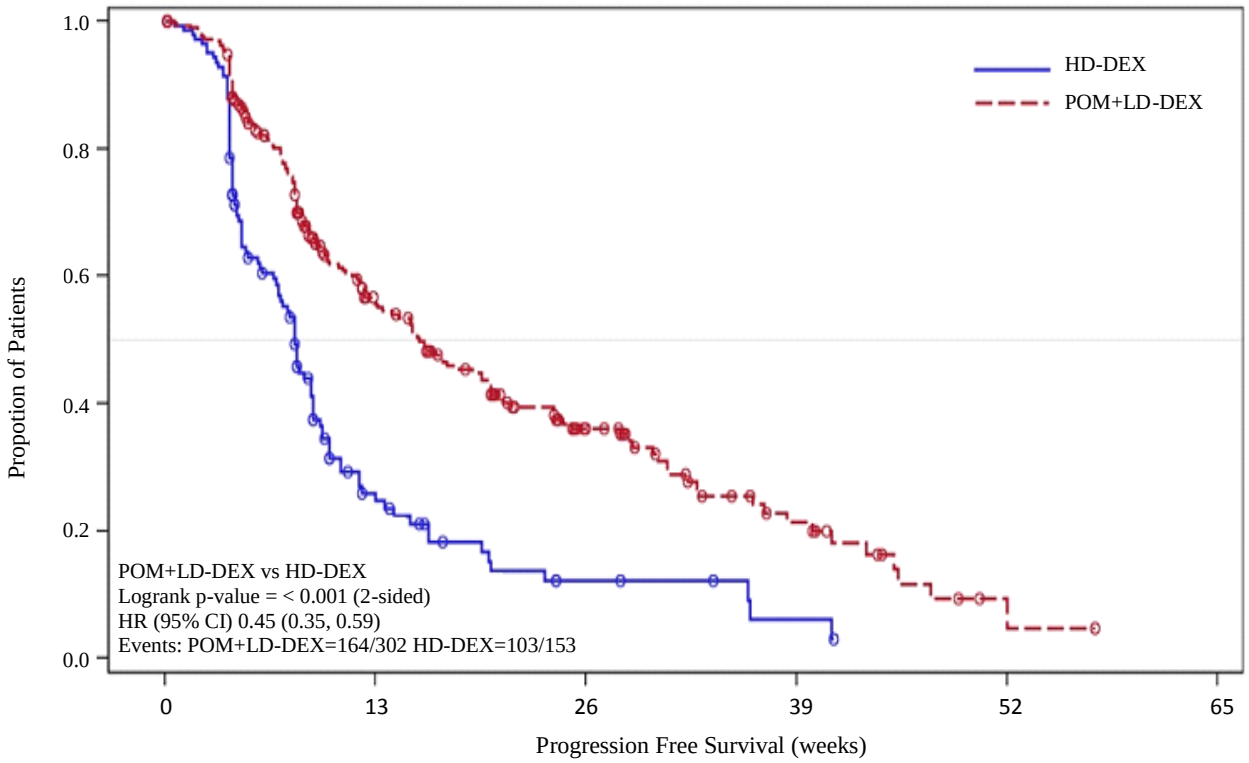
Progression Free Survival is summarised in Table 1 for the ITT population. Kaplan-Meier curve for PFS for the ITT population is provided in Figure 1.

Table 1: 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 drugs), 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 1: 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 2 for the ITT population. Kaplan-Meier curve for OS for the ITT population is provided in Figure 2.

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.

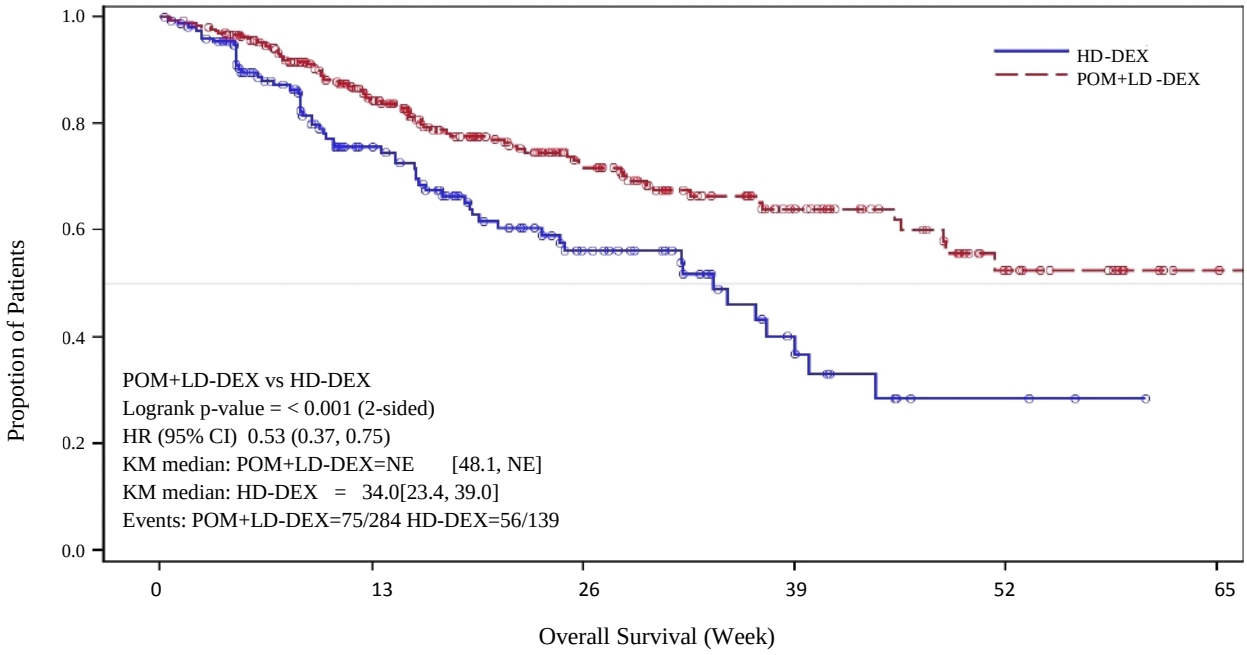
Table 2: Overall Survival: ITT Population

	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)

	Statistics	Pom+LD-Dex (N=302)	HD-Dex (N=153)
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]	
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 2: Kaplan-Meier Curve of Overall Survival (ITT Population)



cutoff: 07 Sep 2012

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Imnovid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

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 drug-drug 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
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 tumors 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
No data are available on administration of pomalidomide to paediatric or adolescent patients (< 18 years of age).

Older people
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 dosage adjustment was required in elderly (> 65 years) patients exposed to pomalidomide. Please 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 normalized AUC exposure to pomalidomide was 98.2% with a 90% confidence interval [77.4% to 120.6%] in moderate renal impairment patients (eGFR ≥30 to ≤45mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% with a 90% confidence interval [79.7% to 127.0%] in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized 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 require dosage 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 dosages 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 dosage 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 dosage 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 dosages ranging from 10 to 250 mg/kg produced embryo-foetal developmental malforma tions. 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 content:
Mannitol
Pregelatinised starch
Sodium stearyl fumarate

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

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 Polyvinyl chloride (PVC)/ polychlorotrifluoroethylene (PCTFE) blisters with push through aluminium foil.

Pack size of 21 capsules.

6.6 Special precautions for disposal and other handling

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

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. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/850/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 3 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 3 mg of pomalidomide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Imnovid 3 mg hard capsule: Dark blue opaque cap and green opaque body, imprinted, "POML 3 mg" in white ink, size 2, hard gelatin capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imnovid 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.

Posology
The recommended starting dose of Imnovid is 4 mg once daily taken orally on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

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

Treatment should be discontinued upon progression of disease.

Pomalidomide dose modification or interruption
Instructions for dose interruptions and reductions for pomalidomide related to haematologic adverse reactions are outlined in the table below:

- *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, follow CBC** weekly.
• ANC return to ≥1 x 10^9/l	Resume pomalidomide treatment at 3 mg daily.
• 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 1 mg less than the previous dose.
Thrombocytopenia • Platelet count <25 x 10^9/l	Interrupt pomalidomide treatment, follow CBC** weekly
• Platelet count return to ≥50 x 10^9/l	Resume pomalidomide treatment at 3 mg daily
• 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 1 mg less than the previous dose

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

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.

In case of neutropaenia, the physician should consider the use of growth factors.

For other Grade 3 or 4 adverse reactions judged to be related to pomalidomide, stop treatment and restart treatment at 1 mg less than the previous dose when an adverse reaction has resolved to ≤ Grade 2 at the physician's discretion.

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

Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, 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, and should not be resumed following discontinuation from these reactions.

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

- *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 decrease one dose level when dose restarted.
Oedema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Restart with dose decreased by one level.
Hyperglycaemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed
Acute pancreatitis	Discontinue patient from dexamethasone treatment regimen.
Other ≥ Grade 3dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤ Grade 2. Resume with dose reduced by one level.

Dexamethasone dose reduction levels:
Dose reduction levels (≤ 75 years of age): Starting dose 40 mg; dose level -1 20 mg; dose level-2 10 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Dose reduction levels (> 75 years of age): Starting dose 20 mg; dose level -1 12 mg; dose level-2 8 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

Special populations

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

Older people
No dose adjustment is required for pomalidomide. For patients >75 years of age, the starting dose of dexamethasone is 20 mg once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

Renal impairment
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 > 2.0 mg/dL 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.

Method of administration
Oral use.
Imnovid should be taken at the same time each day. The capsules should not be opened, broken or chewed (see section 6.6). This medicinal product should be swallowed whole, preferably with water, with or without food. If the patient forgets to take a dose of Imnovid 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*
- 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, 4 weeks before starting treatment, throughout the entire duration of treatment, and 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 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. As a precaution, 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, during treatment and for 7 days after dose interruptions and/or cessation of treatment. Vasectomised males 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.

<u>Contraception</u>
Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 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 method 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 every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
Pomalidomide is present in human semen during treatment. As a precaution, and taking into account special populations with potentially prolonged elimination time such as renal impairment, all male patients taking pomalidomide, including those who have had a vasectomy, 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.
Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for 7 days following discontinuation of pomalidomide.

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 7 days following discontinuation of pomalidomide.

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 therapy 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 in accordance with the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and /or dispensing controls, and the collection of detailed data 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 4 weeks, 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 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.

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 failure events, including congestive cardiac failure and pulmonary oedema (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 failure.

Tumour lysis syndrome
Tumour lysis syndrome may occur.The patients at greatest risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Second Primary Malignancies
Second primary malignancies, such as non-melanoma skin cancer, have been reported in patients receiving 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 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Imnovid on other medicinal products
Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug 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 drug-drug 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 Imnovid
Pomalidomide is partly metabolised by CYP1A2 and CYP3A4/5. It is also a substrate for P-glycoprotein. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased 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 section 4.3 and section 4.4.

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 should be made whether to discontinue nursing or to

discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

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

4.7 Effects on ability to drive and use machines

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

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

The frequencies of adverse reactions are those reported in the pomalidomide plus dexamethasone arm of study CC-4047-MM-003 (n = 302) and from post marketing data. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined in accordance with current guidance, as: very common (≥1/10), common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100).

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

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Metabolism and nutrition disorders	**Very Common** Decreased appetite **Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Tumour lysis syndrome*	**Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Decreased appetite Tumour lysis syndrome*
Psychiatric disorders	**Common** Confusional state	**Common** Confusional state
Nervous system disorders	**Common** Depressed level of consciousness Peripheral sensory neuropathy Dizziness Tremor Intracranial haemorrhage* **Uncommon** Cerebrovascular accident*	**Common** Depressed level of consciousness **Uncommon** Peripheral sensory neuropathy Dizziness Tremor Cerebrovascular accident* Intracranial haemorrhage*
Ear and labyrinth disorders	**Common** Vertigo	**Common** Vertigo
Vascular disorders	**Common** Deep vein thrombosis	**Uncommon** Deep vein thrombosis
Cardiac disorders	**Common** Cardiac failure* Atrial fibrillation* Myocardial infarction*	**Common** Cardiac failure* Atrial fibrillation* **Uncommon** Myocardial infarction*
Immune system disorders	**Common** Angioedema* Urticaria*	**Uncommon** Angioedema* Urticaria*

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea Cough **Common** Pulmonary embolism Epistaxis* Interstitial lung disease*	**Common** Dyspnoea **Uncommon** Pulmonary embolism Cough Epistaxis* Interstitial lung disease*
Gastrointestinal disorders	**Very Common** Diarrhoea Nausea Constipation **Common** Vomiting Gastrointestinal haemorrhage	**Common** Diarrhoea Vomiting Constipation **Uncommon** Nausea Gastrointestinal haemorrhage
Hepatobiliary disorders	**Uncommon** Hyperbilirubinaemia Hepatitis*	**Uncommon** Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	**Common** Rash Pruritus **Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms* Toxic Epidermal Necrolysis* Stevens-Johnson Syndrome*	**Common** Rash **Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms* Toxic Epidermal Necrolysis* Stevens-Johnson Syndrome*
Musculoskeletal and connective tissue disorders	**Very Common** Bone pain Muscle spasms	**Common** Bone pain **Uncommon** Muscle spasms

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Renal and urinary disorders	**Common** Renal failure Urinary retention	**Common** Renal failure **Uncommon** Urinary retention
Reproductive system and breast disorders	**Common** Pelvic pain	**Common** Pelvic pain
General disorders and administration site conditions	**Very Common** Fatigue Pyrexia Oedema peripheral	**Common** Fatigue Pyrexia Oedema peripheral
Investigations	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased Blood uric acid increased*	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased **Uncommon** Blood uric acid increased*

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

Description of selected adverse reactions

Teratogenicity
Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis (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 45.3% of patients who received pomalidomide plus low dose dexamethasone (Pom + LD-Dex), and in 19.5% of patients who received high dose dexamethasone (HD-Dex). Neutropenia was Grade 3 or 4 in 41.7% of patients who received Pom + LD-Dex, compared with 14.8% who received HD-Dex. In Pom + LD-Dex treated patients neutropenia was infrequently serious (2.0% of patients), did not lead to treatment discontinuation, and was associated with treatment interruption in 21.0% of patients, and with dose reduction in 7.7% of patients.

Febrile neutropenia (FN) was experienced in 6.7% of patients who received Pom + LD-Dex, and in no patients who received HD-Dex. All were reported to be Grade 3 or 4. FN was reported to be serious in

4.0% of patients. FN was associated with dose interruption in 3.7% of patients, and with dose reduction in 1.3% of patients, and with no treatment discontinuations.

Thrombocytopenia occurred in 27.0% of patients who received Pom + LD-Dex, and 26.8% of patients who received HD-Dex. Thrombocytopenia was Grade 3 or 4 in 20.7% of patients who received Pom + LD-Dex and in 24.2% who received HD-Dex. In Pom + LD-Dex treated patients, thrombocytopenia was serious in 1.7% of patients, led to dose reduction in 6.3% of patients, to dose interruption in 8% of patients and to treatment discontinuation in 0.7% of patients. (see sections 4.2 and 4.4)

Infection
Infection was the most common non haematological toxicity; it occurred in 55.0% of patients who received Pom + LD-Dex, and 48.3% of patients who received HD-Dex. Approximately half of those infections were Grade 3 or 4; 24.0% in Pom + LD-Dex-treated patients and 22.8% in patients who received HD-Dex.

In Pom + LD-Dex treated patients pneumonia and upper respiratory tract infections were the most commonly reported infections (in 10.7% and 9.3% of patients, respectively);with 24.3% of reported infections being serious and fatal infections (Grade 5) occurring in 2.7% of treated patients. In Pom + LD-Dex treated patients infections led to dose discontinuation in 2.0% of patients, to treatment interruption in 14.3% of patients, and to a dose reduction in 1.3% of patients.

Thromboembolic events
Venous embolic or thrombotic events (VTE) occurred in 3.3% of patients who received Pom + LD-Dex, and 2.0% of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1.3 % of patients who received Pom + LD-Dex, and no patients who received HD-Dex. In Pom + LD-Dex treated patients, VTE was reported as serious in 1.7% of patients, no fatal reactions were reported in clinical studies, and VTE was not associated with dose discontinuation.

Prophylaxis with 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).

Peripheral neuropathy
Patients with ongoing peripheral neuropathy ≥Grade 2 were excluded from clinical studies. Peripheral neuropathy, mostly Grade 1 or 2 occurred in 12.3% patients who received Pom + LD-Dex, and 10.7% of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1.0 % of patients who received Pom + LD-Dex and in 1.3% of patients who received HD-Dex. In patients treated with Pom + LD-Dex, no peripheral neuropathy reactions were reported to have been serious in clinical trials and peripheral neuropathy led to dose discontinuation in 0.3% of patients (see section 4.4).

Median time to onset of neuropathy was 2.1 weeks, varying from 0.1 to 48.3 weeks. Median time to onset was earlier in patients who received HD-Dex compared with Pom + LD-Dex (1.3 weeks versus 2.1 weeks).

Median time to resolution was 22.4 weeks in patients who received Pom + LD-Dex and 13.6 weeks in patients who received HD-Dex. The lower limit of the 95% CI was 5.3 week in the Pom +LD-Dex-treated patients and 2.0 weeks in patients who received HD-Dex.

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 and severe cutaneous reactions including SJS, TEN and DRESS has 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).

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, and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse events related to overdose. Pomalidomide was removed by haemodialysis.

In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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.

Clinical efficacy and safety
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 (PFS) by International Myeloma Working Group (IMWG criteria). For the 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%).

Progression-free survival 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.

Progression Free Survival is summarised in Table 1 for the ITT population. Kaplan-Meier curve for PFS for the ITT population is provided in Figure 1.

Table 1: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.

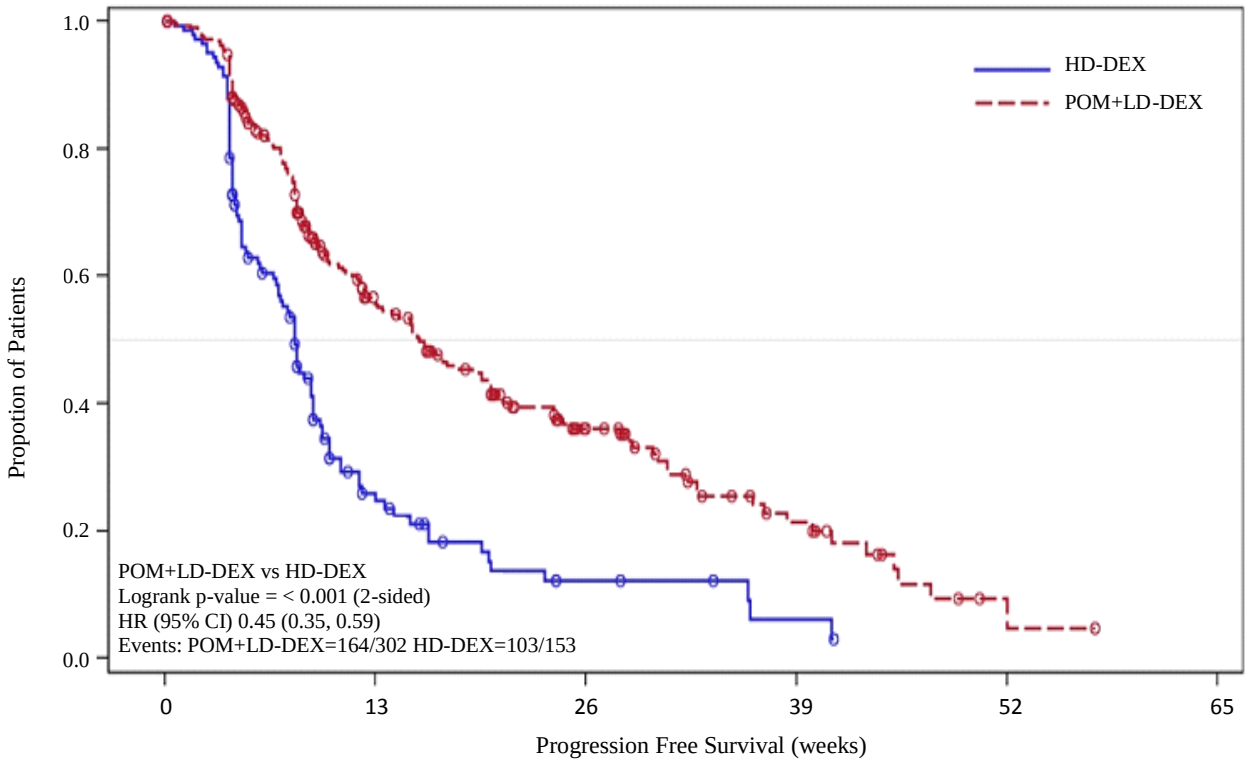
[b] 95% confidence interval about the median progression free survival time.

[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 drugs), 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 1: 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 2 for the ITT population. Kaplan-Meier curve for OS for the ITT population is provided in Figure 2.

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.

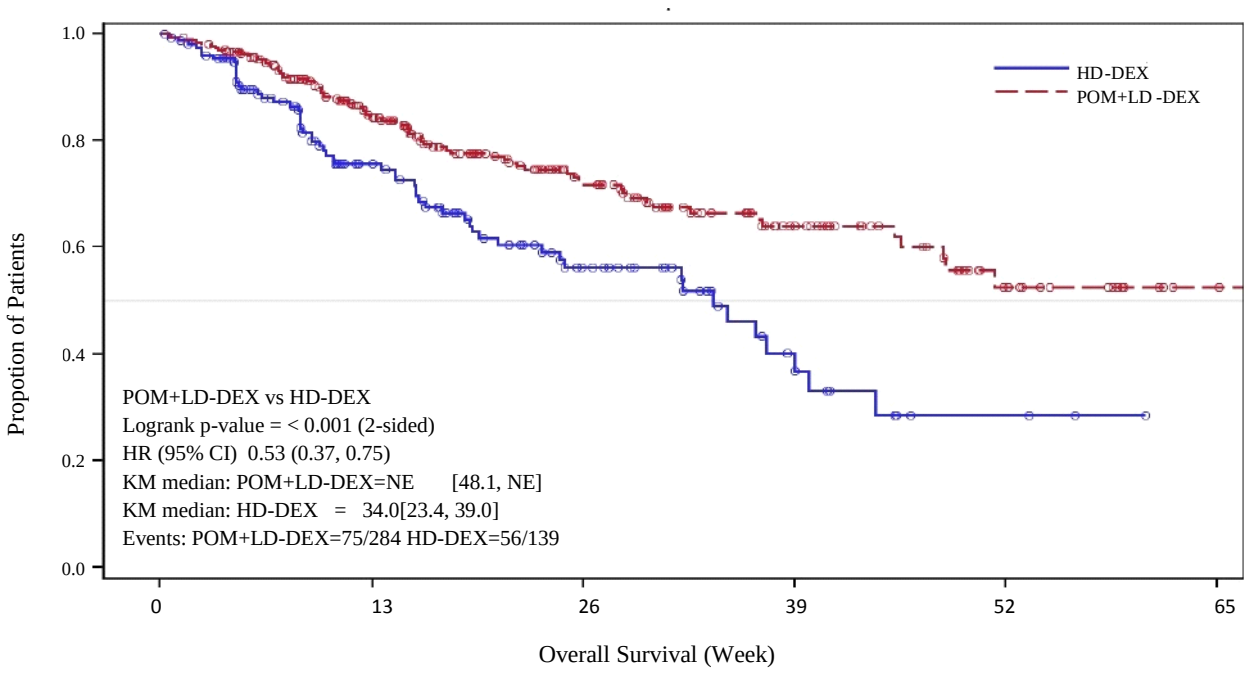
Table 2: Overall Survival: ITT Population

	Statistics	Pom+LD-Dex (N=302)	HD-Dex (N=153)
	N	302 (100.0)	153 (100.0)

	Statistics	Pom+LD-Dex (N=302)	HD-Dex (N=153)
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]	
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 2: Kaplan-Meier Curve of Overall Survival (ITT Population)



cutoff: 07 Sep 2012

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Imnovid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

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 drug-drug 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
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 tumors 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
No data are available on administration of pomalidomide to paediatric or adolescent patients (< 18 years of age).

Older people
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 dosage adjustment was required in elderly (> 65 years) patients exposed to pomalidomide. Please 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 normalized AUC exposure to pomalidomide was 98.2% with a 90% confidence interval [77.4% to 120.6%] in moderate renal impairment patients (eGFR ≥30 to ≤45mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% with a 90% confidence interval [79.7% to 127.0%] in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized 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 require dosage 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 dosages 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 dosage 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 dosage 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 dosages ranging from 10 to 250 mg/kg produced embryo-foetal developmental malforma tions. 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 content:
Mannitol
Pregelatinised starch
Sodium stearyl fumarate

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

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 Polyvinyl chloride (PVC)/ polychlorotrifluoroethylene (PCTFE) blisters with push through aluminium foil.

Pack size of 21 capsules.

6.6 Special precautions for disposal and other handling

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

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. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/850/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 4 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 4 mg of pomalidomide.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.
Imnovid 4 mg hard capsule: Dark blue opaque cap and blue opaque body, imprinted “POML 4 mg” in white ink, size 2, hard gelatin capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Imnovid 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.

Posology
The recommended starting dose of Imnovid is 4 mg once daily taken orally on Days 1 to 21 of repeated 28-day cycles. The recommended dose of dexamethasone is 40 mg orally once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

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

Treatment should be discontinued upon progression of disease.

Pomalidomide dose modification or interruption
Instructions for dose interruptions and reductions for pomalidomide related to haematologic adverse reactions are outlined in the table below:

- *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, follow CBC** weekly.
• ANC return to ≥1 x 10^9/l	Resume pomalidomide treatment at 3 mg daily.
• 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 1 mg less than the previous dose.
Thrombocytopenia • Platelet count <25 x 10^9/l	Interrupt pomalidomide treatment, follow CBC** weekly
• Platelet count return to ≥50 x 10^9/l	Resume pomalidomide treatment at 3 mg daily
• 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 1 mg less than the previous dose

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

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.

In case of neutropaenia, the physician should consider the use of growth factors.

For other Grade 3 or 4 adverse reactions judged to be related to pomalidomide, stop treatment and restart treatment at 1 mg less than the previous dose when an adverse reaction has resolved to ≤ Grade 2 at the physician's discretion.

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

Pomalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, Grade 4 rash, 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, and should not be resumed following discontinuation from these reactions.

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

- *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 decrease one dose level when dose restarted.
Oedema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level.
Muscle weakness ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. Restart with dose decreased by one level.
Hyperglycaemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed
Acute pancreatitis	Discontinue patient from dexamethasone treatment regimen.
Other ≥ Grade 3dexamethasone-related adverse events	Stop dexamethasone dosing until adverse event resolves to ≤ Grade 2. Resume with dose reduced by one level.

Dexamethasone dose reduction levels:
Dose reduction levels (≤ 75 years of age): Starting dose 40 mg; dose level -1 20 mg; dose level-2 10 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
Dose reduction levels (> 75 years of age): Starting dose 20 mg; dose level -1 12 mg; dose level-2 8 mg on Days 1, 8, 15 and 22 of each 28-day treatment cycle.
If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

Special populations

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

Older people
No dose adjustment is required for pomalidomide. For patients >75 years of age, the starting dose of dexamethasone is 20 mg once daily on Days 1, 8, 15 and 22 of each 28-day treatment cycle.

Renal impairment
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 > 2.0 mg/dL 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.

Method of administration
Oral use.
Imnovid should be taken at the same time each day. The capsules should not be opened, broken or chewed (see section 6.6). This medicinal product should be swallowed whole, preferably with water, with or without food. If the patient forgets to take a dose of Imnovid 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*
- 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, 4 weeks before starting treatment, throughout the entire duration of treatment, and 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 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. As a precaution, 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, during treatment and for 7 days after dose interruptions and/or cessation of treatment. Vasectomised males 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.

<u>Contraception</u>
Women of childbearing potential must use one effective method of contraception for 4 weeks before therapy, during therapy, and until 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 method 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 every 4 weeks, including 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 3 days prior to the visit to the prescriber.

Men
Pomalidomide is present in human semen during treatment. As a precaution, and taking into account special populations with potentially prolonged elimination time such as renal impairment, all male patients taking pomalidomide, including those who have had a vasectomy, 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.
Male patients should not donate semen or sperm during treatment (including during dose interruptions) and for 7 days following discontinuation of pomalidomide.

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 7 days following discontinuation of pomalidomide.

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 therapy 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 in accordance with the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and /or dispensing controls, and the collection of detailed data 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 4 weeks, 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 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.

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 failure events, including congestive cardiac failure and pulmonary oedema (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 failure.

Tumour lysis syndrome
Tumour lysis syndrome may occur.The patients at greatest risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Second Primary Malignancies
Second primary malignancies, such as non-melanoma skin cancer, have been reported in patients receiving 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 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.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Imnovid on other medicinal products
Pomalidomide is not anticipated to cause clinically relevant pharmacokinetic drug-drug 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 drug-drug 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 Imnovid
Pomalidomide is partly metabolised by CYP1A2 and CYP3A4/5. It is also a substrate for P-glycoprotein. Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole, increased 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 section 4.3 and section 4.4.

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 should be made whether to discontinue nursing or to

discontinue the medicinal product, taking into account the importance of the medicinal product to the mother.

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

4.7 Effects on ability to drive and use machines

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

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

The frequencies of adverse reactions are those reported in the pomalidomide plus dexamethasone arm of study CC-4047-MM-003 (n = 302) and from post marketing data. Within each SOC and frequency grouping, adverse reactions are presented in order of decreasing seriousness. Frequencies are defined in accordance with current guidance, as: very common (≥1/10), common (≥1/100 to <1/10); and uncommon (≥1/1,000 to <1/100).

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

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Metabolism and nutrition disorders	**Very Common** Decreased appetite **Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Tumour lysis syndrome*	**Common** Hyperkalaemia Hyponatraemia Hyperuricaemia* **Uncommon** Decreased appetite Tumour lysis syndrome*
Psychiatric disorders	**Common** Confusional state	**Common** Confusional state
Nervous system disorders	**Common** Depressed level of consciousness Peripheral sensory neuropathy Dizziness Tremor Intracranial haemorrhage* **Uncommon** Cerebrovascular accident*	**Common** Depressed level of consciousness **Uncommon** Peripheral sensory neuropathy Dizziness Tremor Cerebrovascular accident* Intracranial haemorrhage*
Ear and labyrinth disorders	**Common** Vertigo	**Common** Vertigo
Vascular disorders	**Common** Deep vein thrombosis	**Uncommon** Deep vein thrombosis
Cardiac disorders	**Common** Cardiac failure* Atrial fibrillation* Myocardial infarction*	**Common** Cardiac failure* Atrial fibrillation* **Uncommon** Myocardial infarction*
Immune system disorders	**Common** Angioedema* Urticaria*	**Uncommon** Angioedema* Urticaria*

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Respiratory, thoracic and mediastinal disorders	**Very Common** Dyspnoea Cough **Common** Pulmonary embolism Epistaxis* Interstitial lung disease*	**Common** Dyspnoea **Uncommon** Pulmonary embolism Cough Epistaxis* Interstitial lung disease*
Gastrointestinal disorders	**Very Common** Diarrhoea Nausea Constipation **Common** Vomiting Gastrointestinal haemorrhage	**Common** Diarrhoea Vomiting Constipation **Uncommon** Nausea Gastrointestinal haemorrhage
Hepatobiliary disorders	**Uncommon** Hyperbilirubinaemia Hepatitis*	**Uncommon** Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	**Common** Rash Pruritus **Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms* Toxic Epidermal Necrolysis* Stevens-Johnson Syndrome*	**Common** Rash **Not Known** Drug Reaction with Eosinophilia and Systemic Symptoms* Toxic Epidermal Necrolysis* Stevens-Johnson Syndrome*
Musculoskeletal and connective tissue disorders	**Very Common** Bone pain Muscle spasms	**Common** Bone pain **Uncommon** Muscle spasms

System Organ Class/ Preferred Term	All Adverse Reactions /Frequency	Grade 3−4 Adverse Reactions /Frequency
Renal and urinary disorders	**Common** Renal failure Urinary retention	**Common** Renal failure **Uncommon** Urinary retention
Reproductive system and breast disorders	**Common** Pelvic pain	**Common** Pelvic pain
General disorders and administration site conditions	**Very Common** Fatigue Pyrexia Oedema peripheral	**Common** Fatigue Pyrexia Oedema peripheral
Investigations	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased Blood uric acid increased*	**Common** Neutrophil count decreased White blood cell count decreased Platelet count decreased Alanine aminotransferase increased **Uncommon** Blood uric acid increased*

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

Description of selected adverse reactions

Teratogenicity
Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis (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 45.3% of patients who received pomalidomide plus low dose dexamethasone (Pom + LD-Dex), and in 19.5% of patients who received high dose dexamethasone (HD-Dex). Neutropenia was Grade 3 or 4 in 41.7% of patients who received Pom + LD-Dex, compared with 14.8% who received HD-Dex. In Pom + LD-Dex treated patients neutropenia was infrequently serious (2.0% of patients), did not lead to treatment discontinuation, and was associated with treatment interruption in 21.0% of patients, and with dose reduction in 7.7% of patients.

Febrile neutropenia (FN) was experienced in 6.7% of patients who received Pom + LD-Dex, and in no patients who received HD-Dex. All were reported to be Grade 3 or 4. FN was reported to be serious in

4.0% of patients. FN was associated with dose interruption in 3.7% of patients, and with dose reduction in 1.3% of patients, and with no treatment discontinuations.

Thrombocytopenia occurred in 27.0% of patients who received Pom + LD-Dex, and 26.8% of patients who received HD-Dex. Thrombocytopenia was Grade 3 or 4 in 20.7% of patients who received Pom + LD-Dex and in 24.2% who received HD-Dex. In Pom + LD-Dex treated patients, thrombocytopenia was serious in 1.7% of patients, led to dose reduction in 6.3% of patients, to dose interruption in 8% of patients and to treatment discontinuation in 0.7% of patients. (see sections 4.2 and 4.4)

Infection
Infection was the most common non haematological toxicity; it occurred in 55.0% of patients who received Pom + LD-Dex, and 48.3% of patients who received HD-Dex. Approximately half of those infections were Grade 3 or 4; 24.0% in Pom + LD-Dex-treated patients and 22.8% in patients who received HD-Dex.

In Pom + LD-Dex treated patients pneumonia and upper respiratory tract infections were the most commonly reported infections (in 10.7% and 9.3% of patients, respectively);with 24.3% of reported infections being serious and fatal infections (Grade 5) occurring in 2.7% of treated patients. In Pom + LD-Dex treated patients infections led to dose discontinuation in 2.0% of patients, to treatment interruption in 14.3% of patients, and to a dose reduction in 1.3% of patients.

Thromboembolic events
Venous embolic or thrombotic events (VTE) occurred in 3.3% of patients who received Pom + LD-Dex, and 2.0% of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1.3 % of patients who received Pom + LD-Dex, and no patients who received HD-Dex. In Pom + LD-Dex treated patients, VTE was reported as serious in 1.7% of patients, no fatal reactions were reported in clinical studies, and VTE was not associated with dose discontinuation.

Prophylaxis with 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).

Peripheral neuropathy
Patients with ongoing peripheral neuropathy ≥Grade 2 were excluded from clinical studies. Peripheral neuropathy, mostly Grade 1 or 2 occurred in 12.3% patients who received Pom + LD-Dex, and 10.7% of patients who received HD-Dex. Grade 3 or 4 reactions occurred in 1.0 % of patients who received Pom + LD-Dex and in 1.3% of patients who received HD-Dex. In patients treated with Pom + LD-Dex, no peripheral neuropathy reactions were reported to have been serious in clinical trials and peripheral neuropathy led to dose discontinuation in 0.3% of patients (see section 4.4).

Median time to onset of neuropathy was 2.1 weeks, varying from 0.1 to 48.3 weeks. Median time to onset was earlier in patients who received HD-Dex compared with Pom + LD-Dex (1.3 weeks versus 2.1 weeks).

Median time to resolution was 22.4 weeks in patients who received Pom + LD-Dex and 13.6 weeks in patients who received HD-Dex. The lower limit of the 95% CI was 5.3 week in the Pom +LD-Dex-treated patients and 2.0 weeks in patients who received HD-Dex.

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 and severe cutaneous reactions including SJS, TEN and DRESS has 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).

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, and 10 mg as once-daily multiple doses in multiple myeloma patients have been studied without reported serious adverse events related to overdose. Pomalidomide was removed by haemodialysis.

In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic 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.

Clinical efficacy and safety
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 (PFS) by International Myeloma Working Group (IMWG criteria). For the 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%).

Progression-free survival 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.

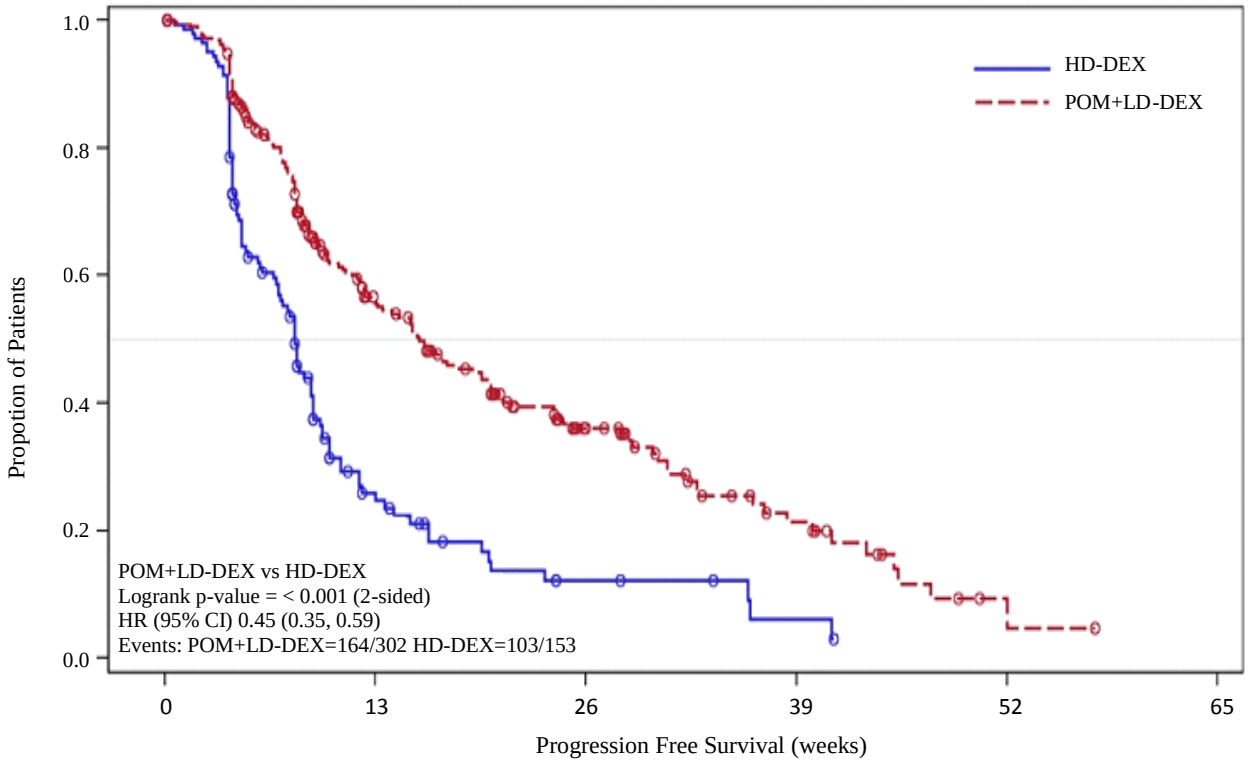
Progression Free Survival is summarised in Table 1 for the ITT population. Kaplan-Meier curve for PFS for the ITT population is provided in Figure 1.

Table 1: 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 drugs), 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 1: 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 2 for the ITT population. Kaplan-Meier curve for OS for the ITT population is provided in Figure 2.

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.

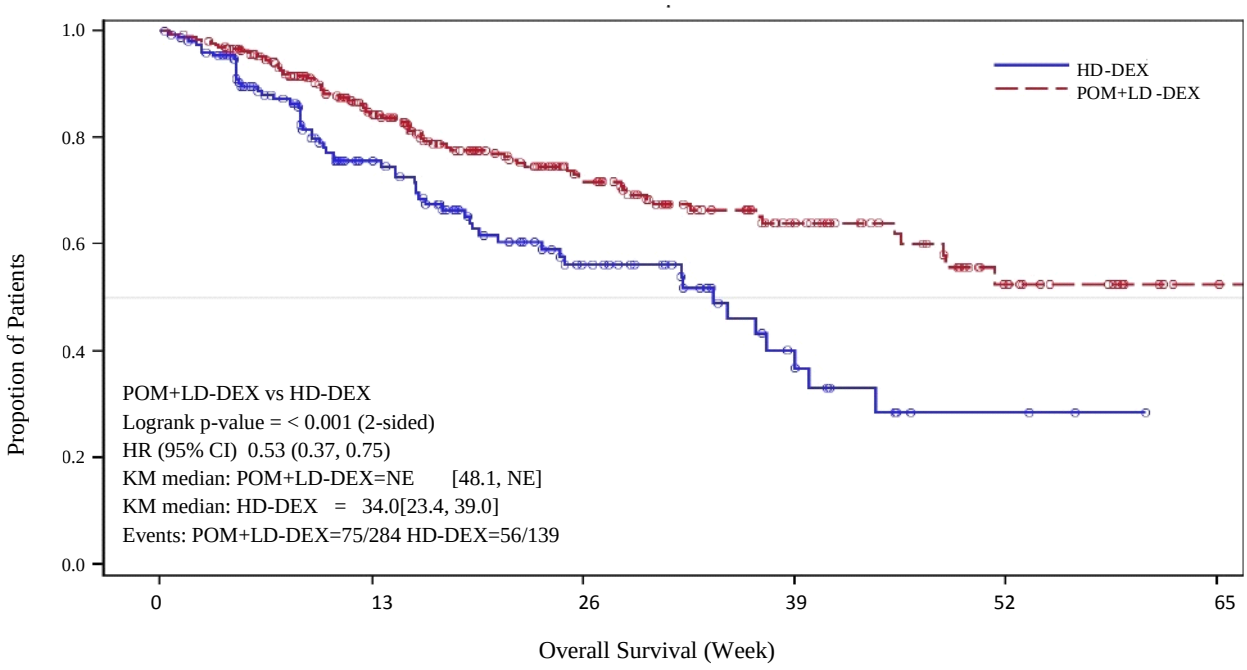
Table 2: Overall Survival: ITT Population

	Statistics	Pom+LD-Dex (N=302)	HD-Dex (N=153)
	N	302 (100.0)	153 (100.0)

	Statistics	Pom+LD-Dex (N=302)	HD-Dex (N=153)
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]	
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 2: Kaplan-Meier Curve of Overall Survival (ITT Population)



cutoff: 07 Sep 2012

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Imnovid in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

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 drug-drug 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
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 tumors 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
No data are available on administration of pomalidomide to paediatric or adolescent patients (< 18 years of age).

Older people
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 dosage adjustment was required in elderly (> 65 years) patients exposed to pomalidomide. Please 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 normalized AUC exposure to pomalidomide was 98.2% with a 90% confidence interval [77.4% to 120.6%] in moderate renal impairment patients (eGFR ≥30 to ≤45mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized AUC exposure to pomalidomide was 100.2% with a 90% confidence interval [79.7% to 127.0%] in severe renal impairment patients not requiring dialysis (CrCl <30 or eGFR <30 mL/minute/1.73 m2) compared to patients with normal renal function. Mean normalized 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 require dosage 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 dosages 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 dosage 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 dosage 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 dosages ranging from 10 to 250 mg/kg produced embryo-foetal developmental malforma tions. 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 content:
Mannitol
Pregelatinised starch
Sodium stearyl fumarate

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

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

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 Polyvinyl chloride (PVC)/ polychlorotrifluoroethylene (PCTFE) blisters with push through aluminium foil.

Pack size of 21 capsules.

6.6 Special precautions for disposal and other handling

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

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. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/850/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 August 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Celgene Europe Limited
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

1. The MAH shall agree the details of a controlled distribution system with the National Competent Authorities and must implement such programme nationally to ensure that:
    - Prior to launch, all doctors who intend to prescribe pomalidomide and all pharmacists who may dispense pomalidomide receive a Direct Healthcare Professional Communication as described below.
    - Prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) pomalidomide are provided with a physician information pack containing the following:
        - Educational Health Care Professional's kit
        - Educational brochures for Patients
        - Patient cards
        - Summary of Product Characteristics (SmPC) and Package Leaflet and Labelling.
2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the marketing of the product.
3. The MAH should agree the final text of the Direct Healthcare Professional Communication and the physician information pack contents with the National Competent Authority in each Member State and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the patient card system in each Member State.
5. The MAH should also agree with each Member State prior to the launch of the product:
    - The set-up of national measures to assess the effectiveness of and compliance with the PPP.

Key elements to be included

Direct Healthcare Professional Communication

The Direct Healthcare Professional Communication shall consist of two parts:

- A core text as agreed by the CHMP.
- National specific requirements agreed with the National Competent Authority regarding:
    - Distribution of the product
    - To ensure that all appropriate measures have been performed prior to pomalidomide being dispensed

The Educational Healthcare Professional's Kit

The Educational Health Care Professional's Kit shall contain the following elements:

- Brief background on pomalidomide and its licensed indication
- Posology
- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Obligations of the health care professional in relation to the prescribing of pomalidomide
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of pomalidomide
    - Need to provide patients with appropriate patient educational brochure and patient card
- Safety advice relevant to all patients
    - Description and management of neutropenia and thrombocytopenia including incidence rates from clinical trials
    - Description and management of thromboembolic risk including incidence rates from clinical trials and post-marketing experience

    - Description and management of infections, dizziness and confusion, tumor lysis syndrome, allergic reactions, hepatic disorders, cardiac failure and interstitial lung disease
    -
    - Disposal of unwanted medicine
    - Local country specific arrangements for a prescription for pomalidomide to be dispensed
    - Explanation of unknown risk of neuropathy with long term use
- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of PPP
    - Definition of women of childbearing potential (WCBP) and actions the physician should take if unsure
- Safety advice for women of childbearing potential
    - The need to avoid foetal exposure
    - Description of the PPP
    - Need for effective contraception (even if woman has amenorrhoea) and definition of effective contraception
        - Pregnancy test regime
        - Advice on suitable tests
        - Before commencing treatment
        - During treatment based on method of contraception
        - After finishing treatment
    - Need to stop pomalidomide immediately upon suspicion of pregnancy
    - Need to tell treating doctor immediately upon suspicion of pregnancy
- Safety advice for men
    - The need to avoid foetal exposure
    - The need to use condoms if sexual partner is pregnant or a WCBP (even if man has had a vasectomy)
        - During pomalidomide treatment
        - For one week following final dose.
    - That he should not donate semen or sperm during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide treatment
    - That if his partner becomes pregnant whilst he is taking pomalidomide or shortly after he has stopped taking pomalidomide he should inform his treating doctor immediately
- Requirements in the event of pregnancy
    - Instructions to stop pomalidomide immediately upon suspicion of pregnancy
    - Need to refer to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy
    - Pregnancy reporting form
- Patient confirmation form ensuring that patients receive the appropriate counselling concerning the treatment, contraceptive methods and pregnancy prevention appropriate for their sex and childbearing status
- Adverse event reporting forms

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential and their partners
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All patient brochures should contain the following elements:

- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans

- That pomalidomide may cause neutropenia and thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Disposal of unwanted medicine
- Guidance on handling pomalidomide for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for pomalidomide to be dispensed
- That the patient should not give pomalidomide to any other person
- That the patient should not donate blood during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide treatment
- That the patient should tell their doctor about any adverse events

The following information should also be provided in the appropriate brochure:

<u>Brochure for women patients with childbearing potential</u>

- The need to avoid foetal exposure
- Description of the PPP
- Need for effective contraception and definition of effective contraception
- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop pomalidomide immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

<u>Brochure for male patients</u>

- The need to avoid fetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP (even if man has had vasectomy)
    - During pomalidomide treatment (including dose interruptions)
    - For 7 days following final dose
- That if his partner becomes pregnant he should inform his treating doctor immediately
- That he should not donate semen or sperm during therapy (including during dose interruptions) and for 7 days after discontinuation of pomalidomide treatment

<u>Patient Card</u>

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Pregnancy test dates and results

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
To conduct a non-interventional post-authorisation registry of patients treated with pomalidomide for relapsed and refractory multiple myeloma to monitor incidence of adverse reactions and to monitor the implementation and compliance of Celgene pregnancy prevention programme and off-label use and controlled distribution system on a country basis in agreement with relevant National Competent Authorities	Final clinical study report: 31 August 2023

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 1 mg hard capsules

pomalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 1 mg of pomalidomide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

WARNING: Risk of severe birth defects. Do not use while pregnant or breastfeeding.
You must follow the Imnovid Pregnancy Prevention Programme.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to the pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/850/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imnovid 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 1 mg hard capsules

pomalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 2 mg hard capsules

pomalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 2 mg of pomalidomide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

WARNING: Risk of severe birth defects. Do not use while pregnant or breastfeeding.
You must follow the Imnovid Pregnancy Prevention Programme.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to the pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/850/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imnovid 2 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 2 mg hard capsules

pomalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 3 mg hard capsules

pomalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 3 mg of pomalidomide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

WARNING: Risk of severe birth defects. Do not use while pregnant or breastfeeding.
You must follow the Imnovid Pregnancy Prevention Programme.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to the pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/850/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imnovid 3 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 3 mg hard capsules

pomalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 4 mg hard capsules

pomalidomide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 4 mg of pomalidomide.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

21 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

WARNING: Risk of severe birth defects. Do not use while pregnant or breastfeeding.
You must follow the Imnovid Pregnancy Prevention Programme.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Unused medicinal product should be returned to the pharmacist.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/13/850/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Imnovid 4 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Imnovid 4 mg hard capsules

pomalidomide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Imnovid 1 mg hard capsules
Imnovid 2 mg hard capsules
Imnovid 3 mg hard capsules
Imnovid 4 mg hard capsules
Pomalidomide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Imnovid is expected to cause severe birth defects and may lead to the death of an unborn baby. Do not take this medicine if you are pregnant or could become pregnant. You must follow the contraception advice described in this leaflet.

Read all of this leaflet carefully before you start taking this medicine - because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse.
- This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Imnovid is and what it is used for

What Imnovid is
Imnovid contains the active substance ‘pomalidomide’. This medicine is related to thalidomide and belongs to a group of medicines which affect the immune system (the body’s natural defences).

What Imnovid is used for
Imnovid is used with another medicine called ‘dexamethasone’ (an anti-inflammatory medicine) to treat adults with a type of cancer called ‘multiple myeloma’. It is used in people whose myeloma has become worse, despite having received at least two other kinds of treatment, including the medicines lenalidomide and bortezomib.

What is multiple myeloma
Multiple myeloma is a type of cancer which affects a certain type of white blood cell (called the 'plasma cell'). These cells grow out of control and accumulate in the bone marrow. This results in damage to the bones and kidneys.

Multiple myeloma generally cannot be cured. However, treatment can reduce the signs and symptoms of the disease, or make them disappear for a period of time. When this happens, it is called 'response'.

How Imnovid works
Imnovid when used with dexamethasone works in a number of different ways:
- by stopping the myeloma cells developing
- by stimulating the immune system to attack the cancer cells
- by stopping the formation of blood vessels supplying the cancer cells.

Imnovid when used with dexamethasone can stop multiple myeloma getting worse:
- On average, Imnovid when used with dexamethasone stopped multiple myeloma from coming back for up to 16 weeks compared with 8 weeks for those patients who used only dexamethasone.

2. What you need to know before you take Imnovid

Do not take Imnovid:
- if you are pregnant or think you may be pregnant or are planning to become pregnant – this is because **Imnovid is expected to be harmful to an unborn child**. (Men and women taking this medicine must read the section "Pregnancy, contraception and breast-feeding – information for women and men" below).
- if you are able to become pregnant, unless you follow all the necessary measures to prevent you from becoming pregnant (see "Pregnancy, contraception and breast-feeding – information for women and men"). If you are able to become pregnant, your doctor will record with each prescription that the necessary measures have been taken and will provide you with this confirmation.
- if you are allergic to pomalidomide or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

If you are uncertain whether any of the conditions above apply to you, talk to your doctor, pharmacist or nurse before taking Imnovid.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Imnovid if:
- you have ever had blood clots in the past. During the treatment with Imnovid you have an increased risk of getting blood clots in your veins and arteries. Your doctor may recommend you take additional treatments (e.g. warfarin) or lower the dose of Imnovid to reduce the chance that you get blood clots.
- you have ever had an allergic reaction such as rash, itching, swelling, feeling dizzy or trouble breathing while taking related medicines called 'thalidomide' or 'lenalidomide'.
- you have had a heart attack, have heart failure, have difficulty breathing, or if you smoke, have high blood pressure or high cholesterol levels.
- you have a high total amount of tumour throughout the body, including your bone marrow. This could lead to a condition where the tumours break down and cause unusual levels of chemicals in the blood which can lead to kidney failure. You may also experience an uneven heartbeat. This condition is called tumour lysis syndrome.
- you have or have had neuropathy (nerve damage causing tingling or pain in your hands or feet).

- you have or have ever had hepatitis B infection. Treatment with Imnovid may cause the hepatitis B virus to become active again in patients who carry the virus, resulting in a recurrence of the infection. Your doctor should check whether you have ever had hepatitis B infection.
- you experience or have experienced in the past a combination of any of the following symptoms: rash on face or extended rash, red skin, high fever, flu-like symptoms, enlarged lymph nodes (signs of severe skin reaction called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or drug hypersensitivity syndrome, Toxic Epidermal Necrolysis (TEN) or Stevens-Johnson Syndrome (SJS). See also section 4 "Possible side effects").

It is important to note that patients with multiple myeloma treated with pomalidomide may develop additional types of cancer, therefore your doctor should carefully evaluate the benefit and risk when you are prescribed this medicine.

At the end of the treatment you should return all unused capsules to the pharmacist.

Pregnancy, contraception and breast-feeding – information for women and men
The following must be followed as stated in the Pomalidomide Pregnancy Prevention Program.
Women and men taking Imnovid must not become pregnant or father a child. This is because pomalidomide is expected to harm the unborn baby. You and your partner should use effective methods of contraception while taking this medicine.

Women
Do not take Imnovid if you are pregnant, think you may be pregnant or are planning to become pregnant. This is because this medicine is expected to harm the unborn baby. Before starting the treatment, you should tell your doctor if you are able to become pregnant, even if you think this is unlikely.

If you are able to become pregnant:
- you must use effective methods of contraception for 4 weeks before starting treatment, for the whole time you are taking treatment, and until 4 weeks after stopping treatment. Talk to your doctor about the best method of contraception for you.
- each time your doctor writes a prescription for you, he will ensure you understand the necessary measures that have to be taken to prevent pregnancy.
- your doctor will arrange pregnancy tests before treatment, every 4 weeks during treatment, and 4 weeks after the treatment has finished

If you become pregnant despite the prevention measures:
- you must stop the treatment immediately and talk to your doctor straight away

Breast-feeding:

It is not known if Imnovid passes into human breast milk. Tell your doctor if you are breast-feeding or intend to breast-feed. Your doctor will advise if you should stop or continue breast-feeding.

Men
Imnovid passes into human semen.
- If your partner is pregnant or able to become pregnant, you must use condoms for the whole time you are taking treatment and for 7 days after the end of treatment.
- If your partner becomes pregnant while you are taking Imnovid, tell your doctor straight away. Your partner should also tell her doctor straight away.

You should not donate semen or sperm during treatment and for 7 days after the end of treatment.

Blood donation and blood tests
You should not donate blood during treatment and for 7 days after the end of treatment.
Before and during the treatment with Imnovid you will have regular blood tests. This is because your medicine may cause a fall in the number of blood cells that help fight infection (white cells) and in the number of cells that help to stop bleeding (platelets).

Your doctor should ask you to have a blood test:
- before treatment
- every week for the first 8 weeks of treatment
- at least every month after that for as long as you are taking Imnovid.

As a result of these tests, your doctor may change your dose of Imnovid or stop your treatment. The doctor may also change the dose or stop the medicine because of your general health.

Children and adolescents
Imnovid is not recommended for use in children and young people under 18 years.

Other medicines and Imnovid
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines. This is because Imnovid can affect the way some other medicines work. Also some other medicines can affect the way Imnovid works.

In particular, tell your doctor, pharmacist or nurse before taking Imnovid if you are taking any of the following medicines:

- some antifungals such as ketaconazole
- some antibiotics (for example ciprofloxacin, enoxacin)
- certain antidepressants such as fluvoxamine.

Driving and using machines
Some people feel tired, dizzy, faint, confused or less alert when taking Imnovid. If this happens to you, do not drive or operate tools or machinery.

3. How to take Imnovid

Imnovid must be given to you by a doctor with experience in treating multiple myeloma.
Imnovid is taken in combination with another medicine called dexamethasone. See the leaflet that comes with dexamethasone for further information on its use and effects.
Always take your medicines exactly as your doctor has told you. Check with your doctor, pharmacist or nurse if you are not sure.

Imnovid and dexamethasone are taken in treatment cycles.
- Each cycle lasts 28 days (4 weeks).

How much to take

Imnovid
The recommended dose of Imnovid is 4 mg per day. In every 4-week cycle, Imnovid should be taken once a day for 3 weeks, followed by a week off. This means:
- Days 1 to 21: take Imnovid once a day.
- Days 22 to 28: do not take Imnovid.

Dexamethasone
The usual starting dose of dexamethasone is 40 mg per day. In every 4-week cycle a dose of dexamethasone should be taken on the first day of each week only. This means:
- Days 1, 8, 15 and 22 of each cycle: take a dose of dexamethasone.
- Days 2 to 7, 9 to 14, 16 to 21 and 23 to 28: do not take dexamethasone.

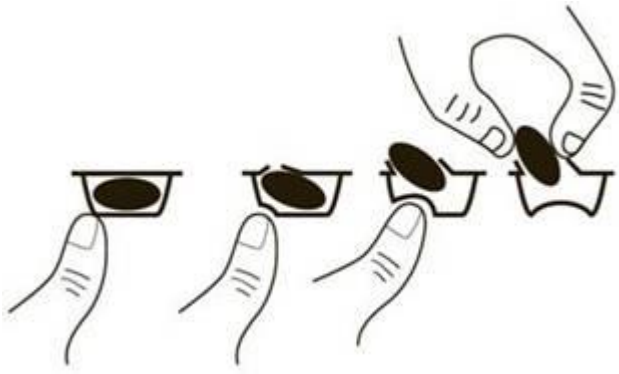
Older patients
For patients above the age of 75 years the usual starting dose of dexamethasone is reduced to 20 mg per day.

After completing each cycle, start a new one.

Your doctor may need to reduce the dose of Imnovid or dexamethasone or stop the treatment based on the results of your blood tests, your general condition, other medications you may be taking (e.g. ciprofloxacin, enoxacin and fluvoxamine) and if you experience side effects (especially rash or swelling) from treatment. If you suffer from liver or kidney problems your doctor will check your condition very carefully whilst you are receiving this medicine.

How and when to take Imnovid
- Do not break, open or chew the capsules. If powder from a broken Imnovid capsule makes contact with the skin, wash the skin immediately and thoroughly with soap and water.
- Swallow the capsules whole, preferably with water.
- You can take the capsules either with or without food.
- Take Imnovid at about the same time each day.

To remove the capsule from the blister, press only one end of the capsule out to push it through the foil. Do not apply pressure on the centre of the capsule as this can cause it to break.



Your doctor will advise you of how and when to take Imnovid if you have kidney problems and are receiving dialysis treatment.

Duration of the treatment with Imnovid
You should continue the cycles of treatment until your doctor tells you to stop.

If you take more Imnovid than you should
If you take more Imnovid than you should, talk to a doctor or go to a hospital straight away. Take the medicine pack with you.

If you forget to take Imnovid
If you forget to take Imnovid on a day when you should, take your next capsule as normal the next day. Do not increase the number of capsules you take to make up for not taking Imnovid the previous day.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Serious side effects which may affect more than 1 in 10 people

Stop taking Imnovid and see a doctor straight away, if you notice any of the following serious side effects – you may need urgent medical treatment
- Fever, sore throat, cough, or any other signs of infection (due to reduced number of white blood cells, which fight infection).
- Bleeding or bruising without a cause, including nosebleeds and bleeding from the bowels or stomach (due to effects on blood cells called 'platelets').
- Chest pain, or leg pain and swelling, especially in your lower leg or calves (caused by blood clots).
- Shortness of breath (from serious chest infection, inflammation of the lung, heart failure or blood clot).
- Swelling of face, lips, tongue and throat, which may cause difficulty breathing (due to a serious type of allergic reaction called angioedema).

Other less common serious side effects
- Recurrence of hepatitis B infection, which can cause yellowing of the skin and eyes, dark brown-coloured urine, right-sided abdominal pain, fever and feeling nauseous or being sick. Tell your doctor straightaway if you notice any of these symptoms.
- Certain types of skin cancer (squamous cell carcinoma and basal cell carcinoma), which can cause changes in the appearance of your skin or growths on your skin. If you notice any changes to your skin whilst taking Imnovid, tell your doctor as soon as possible.

Other side effects
Very common: may affect more than 1 in 10 people
- Infections of the lungs.
- A fall in the number of red blood cells which may cause anaemia leading to tiredness and weakness.
- Loss of appetite.
- Shortness of breath (dyspnoea).
- Constipation, diarrhoea or nausea.
- Muscle spasm, bone pain.
- Swelling of the body, including swelling of the arms or legs.

Common: may affect up to 1 in 10 people
- Bleeding within the skull
- Infections of the nose, sinuses and throat.
- A fast and irregular heartbeat (atrial fibrillation).
- Heart attack (chest pain spreading to the arms, neck, jaw, feeling sweaty and breathless,feeling sick or vomiting).
- Hives (urticaria).

- A fall in the number of red and white blood cells and platelets at the same time (pancytopenia). You will be more prone to bleeding and bruising. You may feel tired and weak, and short of breath. You are also more likely to get infections.
- An infection of the blood caused by bacteria.
- High blood levels of potassium, which can cause abnormal heart rhythm.
- Low blood levels of sodium, which can cause tiredness and confusion, muscle twitching, fits (epileptic seizures) or coma.
- High blood levels of uric acid, which can cause a form of arthritis called gout
- Feeling confused
- Loss of consciousness.
- Numbness, tingling or burning sensation to the skin, pains in hands or feet, dizziness, tremor.
- A spinning feeling in your head, making it difficult to stand up and move normally.
- Vomiting.
- Rashes.
- Itchy skin.
- Kidney failure.
- Inability to pass urine.
- Pain in the pelvis.
- Abnormal liver test.
- Shingles.

Uncommon: may affect up to 1 in 100 people
- Stroke.
- Inflammation of the liver (hepatitis) which can cause itchy skin, yellowing of the skin and the whites of the eyes (jaundice), pale coloured stools, dark coloured urine and abdominal pain.
- The breakdown of cancer cells resulting in the release of toxic compounds into the bloodstream (tumour lysis syndrome). This can result in kidney problems.

Not known (frequency cannot be estimated from the available data):
- Widespread rash, high body temperature, enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS or drug hypersensitivity syndrome, Toxic Epidermal Necrolysis or Stevens-Johnson Syndrome). Stop using pomalidomide if you develop these symptoms and contact your doctor or seek medical attention immediately. See also section 2.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Imnovid

Keep this medicine out of the sight and reach of children.

This medicine does not require any special storage conditions.

Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

Do not use Imnovid if you notice any damage or signs of tampering to medicine packaging.

Do not throw away any medicines via wastewater or household waste. Any unused medicineshould be returned to the pharmacist at the end of treatment. These measures will help protect the environment.

6. Contents of the pack and other information

What Imnovid contains

- The active substance is pomalidomide
- The other ingredients are mannitol, pregelatinised starch, and sodium stearyl fumarate

Imnovid 1 mg hard capsule:

- Each capsule contains 1 mg of pomalidomide.
- The capsule shell contains: gelatin, titanium dioxide (E171), indigotine (E132) and yellow iron oxide (E172) and white and black ink.
- The printing ink contains: shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527) (white ink) and shellac, iron oxide black (E172), propylene glycol (E1520) and ammonium hydroxide (E527) (black ink).

Imnovid 2 mg hard capsule:

- Each capsule contains 2 mg of pomalidomide.
- The capsule shell contains: gelatin, titanium dioxide (E171), indigotine (E132), yellow iron oxide (E172), erythrosin (E127) and white ink.
- The printing ink contains: white ink - shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527).

Imnovid 3 mg hard capsule:

- Each capsule contains 3 mg of pomalidomide.
- The capsule shell contains: gelatin, titanium dioxide (E171), indigotine (E132), yellow iron oxide (E172) and white ink.
- The printing ink contains: white ink - shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527).

Imnovid 4 mg hard capsule:

- Each capsule contains 4 mg of pomalidomide
- The capsule shell contains: gelatin, titanium dioxide (E171), indigotine (E132), brilliant blue FCF (E133), and white ink.
- The printing ink contains: white ink - shellac, titanium dioxide (E171), simethicone, propylene glycol (E1520) and ammonium hydroxide (E527).

What Imnovid looks like and contents of the pack

Imnovid 1 mg hard capsule: Dark blue opaque cap and yellow opaque body, with“POML 1 mg” written on them.
Imnovid 2 mg hard capsule: Dark blue opaque cap and orange opaque body, with“POML 2 mg” written on them.
Imnovid 3 mg hard capsule: Dark blue opaque cap and green opaque body, with“POML 3 mg” written on them.
Imnovid 4 mg hard capsule: Dark blue opaque cap and blue opaque body, with“POML 4 mg” written on them.

Each pack contains 21 capsules.

Marketing Authorisation Holder and Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.