Imnovid® (pomalidomide) Information for Healthcare Professionals

Safety Advice and Pregnancy Prevention Programme Brochure

▼ 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.

Introduction

This Brochure contains the Safety Advice and Pregnancy Prevention Programme (PPP) information needed for prescribing and dispensing Imnovid®. Please also refer to the Summary of Product Characteristics (SmPC).

It is a requirement of the Pregnancy Prevention Programme that all Healthcare Professionals ensure that they have read and understood this Safety Advice and Pregnancy Prevention Programme Brochure before prescribing or dispensing Imnovid® for any patient.

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

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

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. No dose adjustment is required for pomalidomide.

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

The following section contains advice to Healthcare Professionals about how to minimize the main risks associated with the use of pomalidomide.
Please refer also to SmPC (section 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and precautions for use and 4.8 Undesirable effects).

In general, most adverse reactions occurred more frequently during the first 2 to 3 months of treatment.
Please note that the posology, adverse event profile and recommendations outlined herein, particularly in respect of neutropenia and thrombocytopenia, relate to the use of pomalidomide within its licensed indication.
There is currently insufficient evidence regarding safety and efficacy in any other indication.

Management of Neutropenia and Thrombocytopenia

Neutropenia and thrombocytopenia are the major dose-limiting toxicity of treatment with Pomalidomide.

It is therefore encouraged to monitor complete blood counts - including white blood cell count with differential, platelet count, haemoglobin and haematocrit - weekly for the first 8 weeks and monthly thereafter.

A dose modification or interruption may be required. Patients may require use of blood product support and /or growth factors.

Both neutropenia and thrombocytopenia can be managed with dose modifications and/or interruptions
Recommended dose modifications during treatment and restart of treatment with Imnovid® are outlined in the table below:

Dose modification or interruption 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, the platelet count must be ≥ 50 x 10^9/l.

In case of neutropenia, 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.

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 infrequently 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.

Management of Thromboembolic Events

In clinical studies, patients received prophylactic acetylsalicylic acid or alternative anti-thrombotic therapy.

Anti-coagulation therapy unless contraindicated is recommended, (such as acetylsalicylic acid, warfarin, heparin or clopidogrel), especially in patients with additional thrombotic risk factors.

Action should be taken to try to minimize all modifiable risk factors for thromboembolic events (e.g. smoking cessation, control of hypertension and hyperlipidaemia). Patients with known risk factors for thromboembolism including previous history of thrombosis should be closely monitored.

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

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.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to another effective method; refer to the SmPC and the separate Healthcare Professional Brochure on the PPP for further information. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception.

If the patient experiences any thromboembolic events, treatment should be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the pomalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of pomalidomide treatment.

Venous embolic or thrombotic events (VTE) occurred in 3.3% of patients who received POM + LD-Dex, and in 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.

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 common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100).

All Adverse Reactions/Frequency:
Common
Deep vein thrombosis and Pulmonary embolism
Grade 3−4 Adverse Reactions/Frequency:
Uncommon
Deep vein thrombosis and Pulmonary embolism

Infection

Pomalidomide may cause neutropenia, which can make the patient more prone to infections.
Infection was the most common non haematological toxicity; Most of those infections were Grade 3-4 Pneumonia and upper respiratory tract infections were the most commonly reported.

Prophylactic antibiotic therapy (unless contraindicated) should be considered. A decision to take prophylactic measures should be made after a careful assessment of the individual patient's underlying risk factors.

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.

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. 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.

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.

Allergic reaction

Angioedema and severe dermatologic reactions have been reported. 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, Grade 4 rash, exfoliative or bullous rash, and should not be resumed following discontinuation for these reactions.

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. Patients can reduce impact by taking pomalidomide at night.

Interstitial lung disease (ILD)

ILD and related events, including cases of pneumonitis, have been observed with pomalidomide. Onset of respiratory symptoms is usually within 6 months following start of treatment, but there have been cases where the ILD occurred approximately 18 months after starting pomalidomide. ILD usually resolves with steroid treatment and permanent cessation of 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. 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

Cardiac failure

Cases of cardiac failure and related events, which include congestive cardiac failure, acute cardiac failure and acute pulmonary oedema, were observed mainly in patients with existing cardiac disease or risk factors such as hypertension. The majority of these events occurred within 6 months of starting treatment with pomalidomide. Patients with cardiac disease or risk factors should be monitored for signs and symptoms of cardiac failure.

The safety review also concluded that pomalidomide can cause atrial fibrillation, which may precipitate cardiac failure.

Pregnancy Prevention Programme

- This section contains the information needed for prescribing and dispensing Imnovid®, including information about the Pregnancy Prevention Programme (PPP).

- Pomalidomide is structurally related to thalidomide, a known human teratogenic substance that causes severe life-threatening birth defects. Pomalidomide induced, in rats and rabbits, malformations similar to those described with thalidomide.

- If Imnovid® is taken during pregnancy, a teratogenic effect in humans is expected. Imnovid® is therefore contraindicated in pregnancy and in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme described in this pack are carried out.

- All men and all women of childbearing potential should undergo counselling of the need to avoid pregnancy (checklists for counselling are provided at the end of this brochure).

- Treatment Initiation Forms are provided with this Kit. Prior to treating a patient with pomalidomide, it is required that the treating physician and the patient sign a Treatment Initiation Form to confirm that the benefits and risks of pomalidomide therapy have been explained and understood and that the requirements of the Pregnancy Prevention Programme will be complied with. One copy of this form should be given to the patient and the other should be retained in the patient file.

- Patients should be capable of complying with the requirements of safe use of Imnovid®.

- Patients must be provided with the appropriate educational Patient Brochure, Patient Card and a copy of the Treatment Initiation Form.

- Patient Cards to document childbearing status are contained within this Kit. The Patient Card must be signed to confirm counselling has taken place. For women of childbearing potential, the Patient Card will also document the date and results of the monthly pregnancy test. The Patient Card must be completed and a copy provided to the patient. The pharmacist will be required to check the Patient Card for each female patient and verify the correct completion of the Patient Card for each Woman of Childbearing potential prior to each dispense of pomalidomide.

Prescribing Pomalidomide

- For women of childbearing potential, prescriptions of Imnovid® should be limited to 4 weeks of treatment and continuation of treatment requires a new prescription. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of Imnovid® should occur within a maximum of 7 days of either the prescription date or the last pregnancy test date, whichever comes first.

- For all other patients, prescriptions of Imnovid® should be limited to 12 weeks and continuation of treatment requires a new prescription.

- The following are considered to not have childbearing potential.
  - Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*
  - Confirmed premature ovarian failure if confirmed by specialist gynaecologist
  - Previous bilateral salpingo-oophorectomy, or hysterectomy
  - XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy or during lactation does not rule out childbearing potential.

You are advised to refer your patient for a gynaecological opinion if you are unsure whether or not she meets these criteria.

PPP Advice for Women of Child Bearing Potential

- In view of the expected teratogenic risk of Imnovid®, foetal exposure should be avoided.

- Women of childbearing potential (even if they have amenorrhoea) must:
  - use one effective method of contraception for 4 weeks before therapy, during therapy, and until 4 weeks after Imnovid® therapy finished, and even in case of dose interruption or
  - commit to absolute and continuous sexual abstinence

- AND have a medically supervised negative pregnancy test prior to issuing a prescription (with a minimum sensitivity of 25 mIU/ml) once she has been established on contraception for 4 weeks, at 4 weekly intervals during therapy (this includes dose interruptions) and 4 weeks after the end of therapy (unless confirmed tubal sterilisation). This includes those women of childbearing potential who confirm absolute and continued abstinence.

- Patients should be advised to inform the physician prescribing her contraception about the Imnovid® treatment.

- Patients should be advised to inform you if a change or stop of method of contraception is needed.

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 (IUS)
- 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. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during cotreatment with dexamethasone.
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.

- Your patient should be advised that if a pregnancy does occur whilst she is receiving Imnovid®, she must stop treatment immediately and inform her physician immediately.

PPP Advice for Men

- In view of the expected teratogenic risk of Imnovid®, foetal exposure should be avoided.

- Inform your patient which are the effective contraceptive methods that his female partner can use.

- Imnovid® is present in human semen. 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 as

seminal fluid may still contain pomalidomide in the absence of spermatozoa, should use condoms throughout treatment duration, during dose interruption and for 7 days after cessation of treatment if their partner is pregnant or of child bearing 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.

- Patients should be instructed that if their partner becomes pregnant whilst he is taking Imnovid® or 7 days after he has stopped taking Imnovid® he should inform his treating physician immediately. The partner should inform her physician immediately. It is recommended that she be referred to a physician specialised in teratology for evaluation and advice.

Disposal of unwanted medicine

- Patients should be advised never to give Imnovid® to another person and to return any unused capsules to their pharmacist at the end of the treatment.

Blood donation

- All patients should not donate blood during treatment (including dose interruptions) and for 7 days after cessation of treatment with Imnovid®.

Requirements in the event of a suspected pregnancy

- Stop treatment immediately, if female patient.
- Refer patient to a physician specialised or experienced in teratology for evaluation and advice.
    - Notify AM Mangion Ltd of all such occurrences (suspected or confirmed pregnancy or foetal exposure) using the Pregnancy Capture Form is included in this pack:
      AM Mangion Ltd.
      Regulatory Office, "Mangion Building", New Street Off Valletta Road, Luqa.
      Tel: +356 23976333
      Fax: +356 239 76123

      Email : pv@ammangion.com.mt

AM Mangion Ltd will wish to follow-up with you the progress of all pregnancies.

Reporting of Adverse Reactions
Suspected adverse reactions and medication errors should be reported at
ADR Reporting, The Medicines Authority, Post-Licensing Directorate,
Sir Temi Zammit Buildings, Malta Life Sciences Park,
San Gwann SGN 3000, Malta

Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

OR

ADR Reporting: www.medicinesauthority.gov.mt/adrportal

Contact Details

For information and questions on the risk management of Celgene's products, and the Pregnancy Prevention Programme:

AM Mangion Ltd.
Regulatory Office, "Mangion Building", New Street Off Valletta Road, Luqa.
Tel : +356 23976333
Fax: +356 239 76123
Email : pv@ammangion.com.mt

Checklist for Counselling

This checklist is to assist you with counseling a patient before they commence Imnovid® treatment in order to assure it is used safely and correctly. Please choose the applicable column for the risk category of the patient and refer to the counseling messages provided.

Did you inform your patient:	**Male Patients**	**Women of Non-Childbearing Potential***	**Women Childbearing Potential**
• Of the expected teratogenic risk to the unborn child?			
• Of the need for effective contraception** 4 weeks before starting treatment, during treatment interruption, throughout the entire duration of treatment and for 4 weeks after the end of treatment, or absolute and continued abstinence**?**	**N/A**	**N/A**	
• That she must comply with advice on contraception even if she has amenorrhoea**?**	**N/A**	**N/A**	
• Which are the effective contraceptive methods that she or the female partner of a male patient can use?		**N/A**	
• Of the expected consequences of pregnancy and the need to stop treatment and consult rapidly if there is a risk of pregnancy**?**		**N/A**	
• Of the need to use condoms, including those who have had a vasectomy as seminal fluid may still contain pomalidomide in the absence of spermatozoa, throughout treatment duration, during dose interruption, and for 7 days after cessation of treatment if partner is pregnant or of childbearing potential not using effective contraception**?**		**N/A**	**N/A**
• Of the need not to donate semen or sperm during treatment (including during dose interruptions) and for 7 days following discontinuation		**N/A**	**N/A**
• Of the hazards and necessary precautions associated with use of pomalidomide**?**			
• Not to share medication**?**			
• To return unused capsules to pharmacist**?**			
• Not to donate blood whilst taking pomalidomide, during treatment interruptions and for 7 days following discontinuation**?**			
• About the thromboembolic risk and the possible requirement to take thromboprophylaxis during treatment with pomalidomide?			

Can you confirm that your patient:	**Male Patients**	**Women of Non-Childbearing Potential**	**Women Childbearing Potential**
• Was referred to a contraceptive consultant, if required**?**	**N/A**	**N/A**	
• Is capable of complying with contraceptive measures**?**		**N/A**	
• Agreed to undergo pregnancy testing at 4 weekly intervals unless confirmed tubal sterilization**?**	**N/A**	**N/A**	
• Had a negative pregnancy test before starting treatment even if absolute and continued abstinence**?**	**N/A**	**N/A**	•

*Refer to 'Prescribing Pomalidomide' section for criteria to determine if patient is a woman of non-childbearing potential.

** Refer to 'PPP Advice for Women of Child Bearing Potential' section for information on contraception.

TREATMENT FOR A WOMAN OF CHILDBEARING POTENTIAL CANNOT START UNTIL PATIENT IS ESTABLISHED ON EFFECTIVE METHOD OF CONTRACEPTION FOR 4 WEEKS OR COMMITS TO COMPLETE AND CONTINUED ABSTINENCE AND PREGNANCY TEST IS NEGATIVE!

The Pregnancy Prevention Programme is set out in the following Algorithm: