PROFESSIONAL INFORMATION FOR MYLOMID

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MYLOMID 2,5 mg hard capsule.

MYLOMID 5 mg hard capsule.

MYLOMID 7,5 mg hard capsule.

MYLOMID 10 mg hard capsule.

MYLOMID 15 mg hard capsule.

MYLOMID 20 mg hard capsule.

MYLOMID 25 mg hard capsule.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **MYLOMID 2,5 mg** hard capsule contains 2,5 mg lenalidomide.

Contains sugar (lactose anhydrous, 43,33 mg).

Each **MYLOMID 5 mg** hard capsule contains 5 mg lenalidomide.

Contains sugar (lactose anhydrous, 86,67 mg).

Each **MYLOMID 7,5 mg** hard capsule contains 7,5 mg lenalidomide.

Contains sugar (lactose anhydrous, 130,00 mg).

Each **MYLOMID 10 mg** hard capsule contains 10 mg lenalidomide.

Contains sugar (lactose anhydrous, 173,33 mg).

Each **MYLOMID 15 mg** hard capsule contains 15 mg lenalidomide.

Contains sugar (lactose anhydrous, 260,00 mg).

Each **MYLOMID 20 mg** hard capsule contains 20 mg lenalidomide.

Contains sugar (lactose anhydrous, 255,00 mg).

Each **MYLOMID 25 mg** hard capsule contains 25 mg lenalidomide.

Contains sugar (lactose anhydrous, 250,00 mg).

For full list of excipients, see section 6.1

WARNING: SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS:

Lenalidomide is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced malformations in monkeys similar to those described with thalidomide (see section 4.6). If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

BECAUSE OF THIS TOXICITY AND IN AN EFFORT TO MAKE THE CHANCE OF FOETAL EXPOSURE TO MYLOMID AS NEGLIGIBLE AS POSSIBLE, MYLOMID IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME. THIS PROGRAMME IS CALLED THE ACTIVE RISK MANAGEMENT PROGRAM.

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

3. PHARMACEUTICAL FORM

MYLOMID are hard capsules.

MYLOMID 2,5 mg are white/white size “4” capsules printed with NAT on cap and 2,5 mg on body of the capsule, contains off-white to pale yellow coloured powder.

MYLOMID 5 mg are white/white size “2” capsules printed with NAT on cap and 5 mg on body of the capsule, contains off-white to pale yellow coloured powder.

MYLOMID 7,5 mg are white/white size “2” capsules printed with NAT on cap and 7,5 mg on body of the capsule, contains off-white to pale yellow coloured powder.

MYLOMID 10 mg are white/white size “2” capsules printed with NAT on cap and 10 mg on body of the capsule, contains off-white to pale yellow coloured powder.

MYLOMID 15 mg are white/white size “2” capsules printed with NAT on cap and 15 mg on body of the capsule, contains off-white to pale yellow coloured powder.

MYLOMID 20 mg are green/blue size “2” capsules printed with NAT on cap and 20 mg on body of the capsule, contains off-white to pale yellow coloured powder.

MYLOMID 25 mg are white/white size “2” capsules printed with NAT on cap and 25 mg on body of the capsule, contains off-white to pale yellow coloured powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelodysplastic Syndromes (MDS):

MYLOMID is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk Myelodysplastic Syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.

Multiple Myeloma:

MYLOMID in combination with dexamethasone is indicated for the treatment of Multiple Myeloma patients who have received at least one prior therapy.

4.2 Posology and method of administration

Posology

Myelodysplastic Syndromes (MDS):

Recommended dosage:

The recommended starting dose of **MYLOMID** is 10 mg given orally once a day on days 1 – 21 of repeating 28-day treatment cycles.

Recommended dose adjustments during treatment and restart of treatment:

Platelet counts:

Patients who are dosed initially at 10 mg and who experience thrombocytopenia should have their dosage adjusted as follows:

If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg:

If baseline ≥ 100 x 10^9/L	
When platelets:	**Recommended course:**
Fall to < 50 x 10^9/L	Interrupt **MYLOMID** Treatment.
Return to ≥ 50 x 10^9/L	Resume **MYLOMID** at 5 mg once a day continuously in repeating 28 day cycles.

If baseline < 100 x 10^9/L	
When platelets:	**Recommended course:**
Fall to 50 % of the baseline value	Interrupt **MYLOMID** Treatment.
If baseline ≥ 60 x 10^9/L and return to ≥ 50 x 10^9/L	Resume **MYLOMID** at 5 mg once a day continuously in repeating 28 day cycles.
If baseline < 60 x 10^9/L and return to ≥ 30 x 10^9/L	Resume **MYLOMID** at 5 mg once a day continuously in repeating 28 day cycles.

If thrombocytopenia develops AFTER 4 weeks of starting treatment at 10 mg:

When platelets:	**Recommended course:**
< 30 x 10^9/L or < 50 x 10^9/L with platelet transfusions	Interrupt **MYLOMID** Treatment.
Return to ≥ 30 x 10^9/L (without signs of bleeding)	Resume **MYLOMID** at 5 mg once a day continuously in repeating 28 day cycles.

Patients who experience thrombocytopenia at 5 mg daily should have their dosage adjusted as follows:

If thrombocytopenia develops during treatment at 5 mg daily:

When platelets:	**Recommended course:**
< 30 x 10^9/L or < 50 x 10^9/L with platelet transfusions	Interrupt **MYLOMID** Treatment.
Return to ≥ 30 x 10^9/L (without signs of bleeding)	Resume **MYLOMID** at 5 mg every other day.

Neutrophil counts (ANC)$^+$

Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

If neutropenia develops WITHIN 4 weeks of starting treatment at 10 mg:

If baseline ANC ≥ 1 x 10^9/L	
When neutrophils:	**Recommended course:**
Fall to < 0,75 x 10^9/L	Interrupt **MYLOMID** Treatment.
Return to ≥ 1 x 10^9/L	Resume **MYLOMID** at 5 mg once a day continuously in repeating 28 day cycles.

If baseline ANC < 1 x 10^9/L	
When neutrophils:	**Recommended course:**
Fall to < 0,5 x 10^9/L	Interrupt **MYLOMID** Treatment.
Return to ≥ 0,5 x 10^9/L	Resume **MYLOMID** at 5 mg once a day continuously in repeating 28 day cycles.

If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg:

When neutrophils:	**Recommended course:**

< 0,5 x 10^9/L for ≥ 7 days or < 0,5 x 10^9/L associated with fever (≥ 38,5 °C)	Interrupt **MYLOMID** Treatment.
Return to ≥ 0,5 x 10^9/L	Resume **MYLOMID** at 5 mg once a day continuously in repeating 28 day cycles.

+ Absolute neutrophil count.

Patients who experience neutropenia at 5 mg daily should have their dosage adjusted as follows:

If neutropenia develops during treatment at 5 mg daily:

When neutrophils:	**Recommended course:**
< 0,5 x 10^9/L for ≥ 7 days or < 0,5 x 10^9/L associated with fever (≥ 38,5 °C)	Interrupt **MYLOMID** Treatment.
Return to ≥ 0,5 x 10^9/L	Resume **MYLOMID** at 5 mg every other day.

+ Absolute neutrophil count

Other grade 3/4 Toxicities:

For other grade 3/4 toxicities judged to be related to **MYLOMID**, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ grade 2 at the medical practitioner's discretion.

Discontinuation of MYLOMID:

MYLOMID interruption or discontinuation should be considered for grade 2 – 3 skin rash. **MYLOMID** must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation from these reactions.

Multiple Myeloma:

Previously Treated Multiple Myeloma:

Recommended dosage:

The recommended starting dose of **MYLOMID** is 25 mg/day orally on Days 1 – 21 of repeated 28-day cycles for Multiple Myeloma. The recommended dose of dexamethasone is 40 mg/day on Days 1 – 4, 9 – 12 and

17 – 20 of each 28-day cycle for the first 4 cycles of therapy and then 40 mg/day orally on Days 1 – 4 every 28 days.

Treatment should be continued until disease progression or unacceptable toxicity.

Recommended dose adjustments during treatment and restart treatment:

Dose modification guidelines, as summarised below are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia or other grade 3 or 4 toxicity judged to be related to **MYLOMID**.

Platelet counts

Thrombocytopenia:

See table below entitled, '**Dose Reduction Steps for MYLOMID in Previously Treated Multiple Myeloma'**

Neutrophil counts (ANC)

Neutropenia:

See table below entitled, '**Dose Reduction Steps for MYLOMID in Previously Treated Multiple Myeloma**'

Other grade 3/4 Toxicities:

For other grade 3/4 toxicities judged to be related to **MYLOMID**, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ grade 2 at the doctor's discretion.

Discontinuation of MYLOMID:

MYLOMID interruption or discontinuation should be considered from grade 2 – 3 skin rash. **MYLOMID** must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation from these reactions.

Recommended dose adjustment for previously treated Multiple Myeloma:

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

Dose Reduction Steps for MYLOMID in Previously Treated Multiple Myeloma:

Platelet counts

Thrombocytopenia:

When platelets:	**Recommended Course:**	**Dose Levels:**	**Previously Treated Multiple Myeloma (combination with dexamethasone)**
			Days 1 – 21 / 28 day cycle:
Fall to < 30 x 10^9/L	Interrupt **MYLOMID** treatment and follow CBC weekly.	Starting Dose	25 mg
Return to ≥ 30 x 10^9/L	Resume **MYLOMID** at dose level -1.	Dose level -1	15 mg
For each subsequent drop below < 30 x 10^9/L Return to ≥ 30 x 10^9/L	Interrupt **MYLOMID** treatment. Resume **MYLOMID** at the next lower dose level -2 or -3 for the indicated dose regimen. Do not dose below the lowest **MYLOMID** dose level in the indicated dose regimen.	Dose level -2 Dose level -3	10 mg 5 mg

Absolute neutrophil counts (ANC)

Neutropenia:

When neutrophils:	**Recommended Course*:**	**Dose Levels:**	**Previously Treated Multiple Myeloma (combination with dexamethasone):**
Fall to < 0,5 x 10^9/L	Interrupt **MYLOMID** treatment and follow CBC weekly.	Starting Dose	25 mg

Return to ≥ 0,5 x 10^9/L	Resume **MYLOMID** at dose level -1	Dose level -1	15 mg
For each subsequent drop below < 0,5 x 10^9L Return to ≥ 0,5 x 10^9/L	Interrupt **MYLOMID** treatment. Resume **MYLOMID** at the next lower dose level -2 or -3 for the indicated dose regimen. Do not dose below the lowest **MYLOMID** dose level in the indicated dose regimen.	Dose level -2 Dose level -3	10 mg 5 mg

* At the healthcare provider's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of **MYLOMID**.

Other grade 3/4 Toxicities:

For other grade 3/4 toxicities judged to be related to **MYLOMID**, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ grade 2 at the doctor's discretion.

Discontinuation of MYLOMID:

MYLOMID interruption or discontinuation should be considered from grade 2 – 3 skin rash. **MYLOMID** must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation from these reactions.

Paediatrics:

No data are available supporting the use in paediatric patients below the age of 18.

Elderly:

No dose adjustments needed. Because elderly patients are more likely to have decreased renal function, and **MYLOMID** is cleared by the kidney, care should be taken in dose selection (see '**Use in patients with impaired renal function**').

Use in patients with impaired renal function:

MYLOMID is primarily excreted unchanged by the kidney, therefore care should be taken in dose selection, and monitoring of renal function is advised. No dose adjustments are required for patients with creatinine clearance (CLcr) ≥ 60 mL/min. The following **MYLOMID** dose adjustments are recommended at the start of therapy for patients with CLcr < 60 mL/min.

Renal Function (CLcr):	**Starting dose 25 mg:**	**Starting dose 10 mg:**
Moderate Renal Impairment (30 < CLcr < 60 mL/min)	10 mg[a] Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment (CLcr < 30 mL/min, not requiring dialysis)	15 mg Every 48 hours	5 mg Every 48 hours
End Stage Renal Disease (CLcr < 30 mL/min, requiring dialysis)	5 mg Once daily. On dialysis days the dose should be administered following dialysis.	5 mg 3 times a week following each dialysis.

CLcr = creatinine clearance

[a] The dose may be escalated to 15 mg every 24 hours after 2 cycles if the patient is not responding to treatment and is tolerating the medicine.

After initiation of **MYLOMID** therapy, subsequent **MYLOMID** dose modification should be based on individual patient treatment tolerance, as described elsewhere in this section.

Use in Patients with Impaired Hepatic Function:

No study has been conducted in patients with hepatic impairment. **MYLOMID** is not known to be metabolised by the liver; the elimination of unchanged **MYLOMID** is predominantly by the renal route (see section 5.2).

Method of administration:

MYLOMID should be taken orally at about the same time each day.

The capsules should not be opened, broken or chewed. **MYLOMID** capsules should be swallowed whole, preferably with water, either with or without food.

If less than 12 hours has elapsed since missing a dose, the patient can take the dose.
If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day.

Do not take 2 doses at the same time.

4.3 Contraindications

- Hypersensitivity to lenalidomide or any of the excipients.
- Pregnancy and lactation.
- Women of childbearing potential, except when all of the conditions for pregnancy prevention have been met (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

General:

Pregnancy warning:

MYLOMID is contraindicated during pregnancy.

MYLOMID is structurally related to thalidomide.

Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced malformations in monkeys similar to those described with thalidomide (see section 4.6). If **MYLOMID** is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

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

Counselling:

For women of childbearing potential, **MYLOMID** is contraindicated unless all the following are met:

- She understands the expected teratogenic risk to the unborn child.
- She understands the need for effective contraception, without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment including dose interruptions, and at least for 4 weeks after the end of treatment.
- Even if a woman of childbearing potential has amenorrhea 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 **MYLOMID** 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 **MYLOMID**.

For male patients taking **MYLOMID**, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after discontinuation of lenalidomide in the healthy subject (see section 5.2).

As a precaution and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking **MYLOMID** must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.
- Understand 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 (even if the man has had a vasectomy), during treatment and for at least 7 days after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking **MYLOMID** or shortly after he has stopped taking **MYLOMID**, he should inform his doctor immediately and

that it is recommended to refer the female partner to a doctor specialised or experienced in teratology for evaluation and advice.

The prescriber must ensure that for women of childbearing potential:

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

Contraception:

Women of childbearing potential must use two reliable methods of contraception for at least 4 weeks before therapy, during therapy including dose interruptions, and at least until 4 weeks after **MYLOMID** therapy unless the patient commits to absolute and continuous abstinence confirmed on a monthly basis. If not established on effective contraception, the patient must be referred to an appropriately trained healthcare provider for contraceptive advice in order that contraception can be initiated.

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

Highly effective methods:

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

Effective methods:

- Male condom;
- Diaphragm;
- Cervical cap.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking **MYLOMID** and dexamethasone, and in patients with myelodysplastic syndromes taking **MYLOMID** monotherapy, combined oral contraceptive pills are not recommended (see section 4.5).
If a patient is currently using combined oral contraception the patient should switch to two of the effective methods listed above. The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception.
The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (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.

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

Pregnancy testing:

Pregnancy must be excluded by testing blood and/or urine.

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 50 IU/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 **MYLOMID** 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 **MYLOMID** is prescribed or in the 7 days prior to the visit to the prescriber once the patient has been using effective contraception for at least 4 weeks. The test should ensure the patient is not pregnant when she starts treatment with **MYLOMID**

Follow-up and end of treatment:

A medically supervised pregnancy test should be repeated at least every 4 weeks, including at least 4 weeks after the end of treatment, except in the case of confirmed tubal sterilisation. These pregnancy tests should be performed on the day of the prescribing visit or in the 7 days prior to the visit to the prescriber.

Male fertility:

MYLOMID is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after discontinuation of **MYLOMID** in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients should use condoms throughout treatment duration, during dose interruption and for 4 weeks after cessation of treatment if their partner is of childbearing potential and is not established on suitable contraception (even if the male patient has undergone a vasectomy). Male patients taking **MYLOMID** should not donate sperm or semen during treatment including dose interruptions and for 4 weeks following the end of treatment.

Patients should be instructed never to give this medicine to another person and to return any unused capsules to their pharmacist at the end of treatment for safe disposal.

Patients should not donate blood during therapy or for 4 weeks following discontinuation of **MYLOMID**.

Educational materials, prescribing and dispensing restrictions:

In order to assist patients in avoiding foetal exposure to **MYLOMID**, educational material will be provided to healthcare providers to reinforce the warnings about the expected teratogenicity to **MYLOMID**, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. Full patient information about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Active Risk Management Program should be given by the doctor to women of childbearing potential and, as appropriate, to male patients. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of **MYLOMID** to women of childbearing potential should occur within 7 days of the prescription and following a medically supervised negative pregnancy test result.

Prescriptions for women of childbearing potential can be for a maximum duration of treatment of 4 weeks, and prescriptions for all other patients can be for a maximum duration of treatment of 12 weeks.

Other special warnings and precautions for use:

- ***Myocardial infarction:***

  Myocardial infarction has been reported in patients receiving **MYLOMID**, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors, including prior thrombosis, should be closely monitored, and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

- ***Venous and arterial thromboembolic events:***

  In patients with Multiple Myeloma, the combination of **MYLOMID** with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep venous thrombosis and pulmonary embolism). The risk of venous thromboembolism was seen to a lesser extent with **MYLOMID** in combination with melphalan and prednisone.

  In patients with Multiple Myeloma and myelodysplastic syndromes, treatment with **MYLOMID** monotherapy was associated with a lower risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) than in patients with Multiple Myeloma treated with **MYLOMID** in combination therapy.

  In patients with Multiple Myeloma, the combination of **MYLOMID** with dexamethasone is associated with an increased risk of arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event) and was seen to a lesser extent with **MYLOMID** in combination with melphalan and prednisone. The risk of arterial thromboembolism is lower in patients with Multiple Myeloma treated with **MYLOMID** monotherapy than in patients with Multiple Myeloma treated with **MYLOMID** in combination therapy.

Consequently, 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). Concomitant administration of erythropoietic medicines or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic medicines, or other medicines that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in Multiple Myeloma patients receiving **MYLOMID** with dexamethasone. A haemoglobin concentration above 12 g/dL should lead to discontinuation of erythropoietic medicine.

Patients and healthcare providers 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. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors. The decision to take antithrombotic prophylactic measures should be made after careful assessment of an individual patient's underlying risk factors.

If the patient experiences any thromboembolic events, treatment must 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 **MYLOMID** treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of **MYLOMID** treatment.

- ***Neutropenia and thrombocytopenia:***

  The major dose limiting toxicities of **MYLOMID** include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential count, platelet count, haemoglobin, and haematocrit should be performed at baseline, every week for the first 8 weeks of **MYLOMID** treatment and monthly thereafter to monitor for cytopenias.

In case of neutropenia, the doctor should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes, a treatment interruption and/or reduction may be required (see section 4.2).

Patients and doctors are advised to be observant for signs and symptoms of bleeding, including petechiae and epistaxis, especially in patients receiving concomitant medicines susceptible to induce bleeding.

Co-administration of **MYLOMID** with other myelosuppressive medicines should be undertaken with caution.

- ***Multiple myeloma:***

  Patients with at least one prior combination therapy of **MYLOMID** with dexamethasone in Multiple Myeloma patients, with at least one prior therapy, is associated with a higher incidence of grade 4 neutropenia.

  The combination of **MYLOMID** with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 3 and grade 4 thrombocytopenia.

- ***Myelodysplastic Syndromes:***

  MYLOMID treatment in Myelodysplastic Syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia.

- ***Thyroid disorders:***

  Cases of hypothyroidism and cases of hyperthyroidism have been reported. Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

- ***Peripheral neuropathy:***

MYLOMID is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with **MYLOMID** in combination with dexamethasone or melphalan and prednisone or **MYLOMID** monotherapy. The combination of **MYLOMID** with intravenous bortezomib and dexamethasone in Multiple Myeloma patients is associated with a higher frequency of peripheral neuropathy.

- ***Tumour Lysis Syndrome and Tumour Flare Reaction:***

  Tumour Lysis Syndrome (TLS) and Tumour Flare Reaction (TFR) have been observed in patients with Chronic Lymphocytic Leukaemia (CLL), and in patients with other lymphomas, who were treated with **MYLOMID**. Fatal instances of TLS have been reported during treatment with **MYLOMID**. Patients at risk for TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to **MYLOMID**. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been reports of TLS in patients with Multiple Myeloma (MM) treated with **MYLOMID**, and no reports in patients with MDS.

- ***Allergic reactions:***

  Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with **MYLOMID** (see section 4.8). Patients who had previous allergic reactions while treated with thalidomide should be monitored closely, as a possible cross-reaction between **MYLOMID** and thalidomide has been reported.

- ***Severe skin reactions:***

  Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Patients should be advised of the signs and symptoms of these reactions by their doctors and should be told to seek medical attention immediately if they develop these symptoms. **MYLOMID** must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Patients with prior history of grade 4 rash associated with thalidomide treatment

should not receive **MYLOMID**. **MYLOMID** interruption or discontinuation should be considered for grade 2-3 skin rash.

- ***Second Primary Malignancies:***

  An increase of Second Primary Malignancies (SPM) has been observed in previously treated myeloma patients receiving **MYLOMID**/dexamethasone. Non-invasive SPM comprise basal cell or squamous cell skin cancers. Most of the invasive SPMs were solid tumour malignancies.

  Carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as appropriate.

- ***Progression to Acute Myeloid Leukaemia in low- and intermediate 1-risk MDS:***

  Karyotype:

  Baseline variables including complex cytogenetics are associated with progression to Acute Myeloid Leukaemia (AML) in patients who are transfusion dependent and have a del (5q) abnormality. As a consequence, the benefit/risk ratio of lenalidomide when MDS is associated with del (5q) and complex cytogenetics is unknown. A complete blood cell count, including white blood cell count with differential, platelet count, haemoglobin, and haematocrit should be performed weekly for first 8 weeks of **MYLOMID** treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2).

- ***Hepatic disorders:***

  Hepatic failure, including fatal cases, has been reported in patients treated with **MYLOMID** in combination therapy: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe drug-induced hepatotoxicity remains unknown although, in some cases, pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics might be risk factors.

  Abnormal liver function tests were reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

MYLOMID is excreted by the kidneys. It is important to dose adjust patients with renal impairment in order to avoid plasma levels which may increase the risk for higher haematological adverse reactions or hepatotoxicity. Monitoring of liver function is recommended, particularly when there is a history of/or concurrent viral liver infection or when **MYLOMID** is combined with medicines known to be associated with liver dysfunction.

- ***Infection with or without neutropenia****:*

  Patients with Multiple Myeloma are prone to develop infections including pneumonia. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (e.g. cough, fever, etc.) thereby allowing for early management to reduce severity.

- ***Viral reactivation:***

  Cases of viral reactivation have been reported in patients receiving **MYLOMID**, including serious cases of herpes zoster or hepatitis B virus (HBV) reactivation.

  Some of the cases of viral reactivation had a fatal outcome.

  Some of the cases of herpes zoster reactivation resulted in disseminated herpes zoster, meningitis herpes zoster or ophthalmic herpes zoster requiring a temporary hold or permanent discontinuation of the treatment with **MYLOMID** and adequate antiviral treatment.

  Reactivation of hepatitis B has been reported in patients receiving **MYLOMID** 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 **MYLOMID** and adequate antiviral treatment. Hepatitis B virus status should be established before initiating treatment with **MYLOMID**. For patients who test positive for HBV infection, consultation with a doctor with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when **MYLOMID** is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

- ***Progressive Multifocal Leukoencephalopathy:***

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

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

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

- ***Cataract:***

  Cataract has been reported with a higher frequency in patients receiving **MYLOMID** in combination with dexamethasone particularly used for a prolonged time. Regular monitoring of visual ability is recommended.

Excipient warnings:

MYLOMID capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **MYLOMID**.

4.5 Interaction with other medicines and other forms of interaction

Lenalidomide is not a substrate, inhibitor or inducer of cytochrome P450 enzymes *in vitro.* Hence, co-administration of cytochrome P450 substrates or inhibitors with **MYLOMID** is not likely to result in clinically relevant medicine interactions.

Warfarin:

Co-administration of multiple doses of 10 mg of **MYLOMID** had no effect on the single dose pharmacokinetics and pharmacodynamics of R- and S-warfarin. Co-administration of single 25 mg dose of warfarin had no effect on the pharmacokinetics of **MYLOMID**. It is not known whether there is an interaction during concomitant treatment with dexamethasone. Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during treatment.

Digoxin:

When digoxin was co-administered with **MYLOMID** (10 mg/day) the digoxin C_{max} and $AUC_{0-\infty}$ were 14 % higher than when digoxin was administered concomitantly with placebo. Periodic monitoring of digoxin plasma levels is recommended during administration of **MYLOMID**.

Dexamethasone:

In patients with Multiple Myeloma, co-administration of single or multiple doses of dexamethasone (40 mg/day) had no significant effect on the multiple dose pharmacokinetics of **MYLOMID** (25 mg/day).

Interactions with P-glycoprotein (P-gp) inhibitors:

In vitro, **MYLOMID** is a weak substrate, but is not an inhibitor of P-glycoprotein (P-gp).

Interactions with transporters:

In vitro studies demonstrate that **MYLOMID** is not a substrate of human multidrug resistance protein MRP1, MRP2 or MRP3 efflux transporters as well as human organic anion and cation uptake transporters OAT1, OAT3, OATP1B1(OATP2) or OCT1.

Erythropoietic medicines, or other medicines that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in Multiple Myeloma patients receiving MYLOMID with dexamethasone (see section 4.4 and 4.8).

Venous thromboembolic events:

Patients with Multiple Myeloma taking **MYLOMID** and dexamethasone, patients with MDS taking **MYLOMID** monotherapy, as well as patients taking combined oral contraceptive pills or hormone replacement therapy, have an increased risk of venous thromboembolic events (VTE).

Oral contraceptives:

No interaction study has been performed with oral contraceptives. **MYLOMID** is not an enzyme inducer. In an *in vitro* study with human hepatocytes, **MYLOMID**, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if **MYLOMID** is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

Statins:

There is an increased risk of rhabdomyolysis when statins are administered with **MYLOMID**, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

4.6 Fertility, pregnancy and lactation

MYLOMID is contraindicated in females who are pregnant or who could become pregnant.

Pregnancy:

MYLOMID is teratogenic to animals. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore:

- Females of childbearing potential must use effective means of contraception for 28 days before therapy, during **MYLOMID** therapy including dose interruptions, and for 28 days following discontinuation of **MYLOMID** therapy, or continually abstain from sexual intercourse. There is an increased risk of VTE in patients with Multiple Myeloma taking **MYLOMID** and dexamethasone, and

in patients with MDS taking **MYLOMID** monotherapy, and an increased risk of VTE in patients taking combined oral contraceptive pills.

- Females of childbearing potential should undergo regular pregnancy testing during treatment with **MYLOMID**.

- If pregnancy does occur during treatment, **MYLOMID** should be immediately discontinued.

Males:

- Clinical data has demonstrated the presence of lenalidomide, as in **MYLOMID**, in human semen. Therefore, male patients taking **MYLOMID** should use a condom during **MYLOMID** therapy including dose interruptions and for 4 weeks after cessation of treatment. Male patients taking **MYLOMID** should not donate sperm or semen during treatment including dose interruptions and for 4 weeks following the discontinuation of treatment.

Criteria for women of non-childbearing potential:

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

- Age ≥ 50 years and naturally amenorrhoeic for ≤ 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 breastfeeding does not rule out childbearing potential.

Lactation:

Breastfeeding is contraindicated during therapy with **MYLOMID**.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed.

MYLOMID may affect the ability to drive and use machines.

Fatigue, dizziness, somnolence and blurred vision have been reported with the use of **MYLOMID**. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

System Organ Class:	**Frequency:**	**Side effect:**
Infections and Infestations	Frequent	Pneumonia[@], bronchitis, bacterial, viral and fungal infections (including opportunistic infections), upper respiratory tract infection, sinusitis, neutropenic infection, nasopharyngitis, rhinitis, lower respiratory tract infection, pharyngitis, sepsis, enterocolitis infection
	Frequency unknown	Viral infections, including herpes zoster and hepatitis B virus reactivation
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequent	B-cell lymphomas, acute myeloid leukaemia, myelodysplastic syndrome
	Less frequent	Basal cell carcinoma, squamous skin cancer, T-cell type acute leukaemia, tumour lysis syndrome
Blood and lymphatic system disorders	Frequent	Neutropenia[%], thrombocytopenia[@], anaemia[@], leukopenia, febrile

		neutropenia[%], lymphopenia, haemorrhagic disorder, pancytopenia, haemolytic anemia
	Less frequent	Haemolysis, autoimmune haemolytic anemia, hypercoagulation, coagulopathy
	Frequency unknown	Acquired haemophilia
Immune system disorders	Less frequent	Hypersensitivity
	Frequency unknown	Solid organ transplant rejection
Endocrine disorders	Frequent	Hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	Frequent	Decreased appetite, hypokalaemia, hypocalcaemia, dehydration, hypomagnesaemia, iron overload, hypophosphataemia, hyperglycaemia, hypoglycaemia, hyponatraemia, hyperuricaemia, hypercalcaemia, diabetes mellitus, gout
Psychiatric disorders	Frequent	Depression, altered mood, insomnia

	Less frequent	Loss of libido
Nervous system disorders	Frequent	Peripheral neuropathies (excluding motor neuropathy), dizziness, tremor, dysgeusia, headache, lethargy, paraesthesia, syncope, cerebrovascular accident[@], ataxia, balance impaired, neuralgia, dysaesthesia
	Less frequent	Intracranial haemorrhage, transient ischaemic attack, cerebral ischemia
Eye disorders	Frequent	Blurred vision, cataracts, reduced visual acuity
	Less frequent	Blindness
Ear and labyrinth disorders	Frequent	Deafness (including hypoacusis), tinnitus
Cardiac disorders	Frequent	Acute myocardial infarction[@], atrial fibrillation[@], tachycardia, cardiac failure[@], congestive cardiac failure[@], bradycardia, myocardial ischemia
	Less frequent	Dysrhythmia, QT prolongation, atrial flutter, ventricular extrasystoles
Vascular disorders	Frequent	Venous thromboembolic events, predominantly deep

		vein thrombosis and pulmonary embolism@, hypertension, hypotension, haematoma, ecchymosis, vasculitis
	Less frequent	Ischemia, peripheral ischemia, Intracranial venous sinus thrombosis
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, epistaxis, respiratory distress@, cough, rhinorrhea, dysphonia
	Frequency unknown	Interstitial pneumonitis
Gastrointestinal disorders	Frequent	Diarrhoea@, vomiting@, nausea@, constipation, abdominal pain (including upper)@, dry mouth, dyspepsia, toothache, stomatitis, dysphagia
	Less frequent	Colitis, caecitis
	Frequency unknown	Pancreatitis, gastrointestinal perforation (including diverticular, intestinal and large intestine perforations)
Hepato-biliary disorders	Frequent	Abnormal liver function tests, increased alanine aminotransferase, increased aspartate aminotransferase,

		hyperbilirubinaemia, cholestasis, hepatotoxicity
	Less frequent	Hepatic failure
	Frequency unknown	Acute hepatic failure, hepatitis toxic, cytolytic hepatitis, cholestatic hepatitis, mixed cytolytic/cholestatic hepatitis
Skin and subcutaneous tissue disorders	Frequent	Rash[+], pruritus, dry skin, hyperhidrosis, urticaria, skin hyperpigmentation, eczema, erythema
	Less frequent	Skin discolouration, photosensitivity reaction, angioedema, Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN)
	Frequency unknown	Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal, and connective tissue disorders	Frequent	Musculoskeletal and connective tissue pain and discomfort (including back pain and pain in extremity), bone pain, muscle spasms, arthralgia, myalgia, muscle

		weakness, joint swelling
Renal and urinary disorders	Frequent Less frequent	Renal failure@ (including acute), haematuria, urinary retention, urinary incontinence Acquired Fanconi syndrome, renal tubular necrosis
Reproductive system and breast disorders	Frequent	Erectile dysfunction
General disorders and administration site conditions	Frequent	Pyrexia, oedema (including peripheral), influenza like illness syndrome (including pyrexia, cough, rhinitis, myalgia, musculoskeletal pain, pharyngitis, headache and rigors), fatigue, asthenia, chest pain, fall, lethargy, increased blood alkaline phosphatase, increased C-reactive protein, contusion
Investigations	Frequent	Decreased weight

@ - ADRs with Death as an outcome.

% - ADRs which were considered to be Life Threatening (if the outcome of the event was death, it is included with death cases).

- All PRs under SOC of Infections except for rare infections of Public Health interest will be considered listed.

+ - All PTs under HLT of Rash will be considered listed.

Hepatic Disorders:

Transient liver laboratory abnormalities (predominantly transaminases) were reported in patients treated with **MYLOMID**. Treatment with **MYLOMID** should be interrupted and restarted once the levels return to

baseline. Successful re-challenge without recurrence of liver laboratory elevation was reported in some patients.

Reporting of suspected adverse reactions:

Reporting of suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no specific experience in the management of **MYLOMID** overdose in patients. The dose-limiting toxicity is essentially haematogical. In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

A32 Other – Immunomodulators

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

5.1 Pharmacodynamic Properties:

Lenalidomide is an oral immunomodulating medicine with a pleiotropic mechanism of action involving direct tumouricidal activity, immunomodulation, pro-erythropoiesis, and anti-angiogenesis.

Lenalidomide inhibits proliferation of certain haematopoietic tumour cells (including multiple myeloma plasma tumour cells and those with deletions of chromosome 5) and induces expression of tumour suppressor genes, leading to cell cycle arrest. Immunomodulatory properties of lenalidomide include activation of T cells and natural killer (NK) cells, increased numbers of NK T cells, and inhibition of pro-inflammatory cytokines (e.g. TNF-α and IL-6) by monocytes. Pro-erythropoietic properties of lenalidomide include expansion of CD34+ haematopoietic stem cells and increased foetal haemoglobin production. In multiple myeloma cells, the combination of lenalidomide and dexamethasone induces expression of tumour suppressor genes, activates caspases involved in apoptosis, and synergistically inhibits MM cell proliferation.

In myeloplastic syndromes (MDS) (del 5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing apoptosis of del (5q) cells. Sensitivity to lenalidomide in MDS del (5q) can, at least in part, be explained by upregulation of genes (e.g. SPARC, p21, RPS14) which have reduced expression due to haploinsufficiency caused by del (5q).

Cardiac Electrophysiology:

A QTc study was conducted to evaluate the effects of lenalidomide on QT interval at single doses of 10 mg and 50 mg. A single dose of lenalidomide up to 50 mg is not associated with prolongation of the QT interval in healthy male subjects.

5.2 Pharmacokinetic Properties

Absorption:

Lenalidomide, in healthy volunteers, is rapidly absorbed following oral administration with the maximum plasma concentration (C_{max}) occurring between 0,5 and 1,5 hours post dose. The pharmacokinetic disposition of lenalidomide is linear. C_{max} and AUC increase proportionally with increases in dose. Multiple dosing at the recommended dose-regimen does not result in lenalidomide accumulation.

Co-administration with high-fat and high-calorie meal in healthy volunteers reduces the extent of absorption, resulting in an approximately 20 % decrease in area under the concentration versus time curve (AUC) and 50 % decrease in C_{max} in plasma. In the pivotal multiple myeloma and MDS registration trials where the efficacy and safety were investigated for lenalidomide, it was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

In Multiple Myeloma patients (baseline serum creatinine level ≤ 1,5 mg/dL), C_{max} occurs between 0,5 to 6 hours post dose. Plasma exposure (AUC and C_{max}) increases proportionally with dose following single and multiple doses. Multiple doses at 25 mg/day do not cause lenalidomide to accumulate in plasma. Exposure (AUC) in Multiple Myeloma patients is higher compared to healthy volunteers since lenalidomide clearance is lower in these patients than in healthy volunteers. This is consistent with the compromised renal function in the Multiple Myeloma patients (dose adjustments are recommended for patients with CLcr < 60 mL/min; see section 4.2).

In patients with low – or intermediate 1-risk MDS, a single 10 mg oral dose of lenalidomide is rapidly absorbed with the C_{max} observed at around 1 hour post dose. There is no accumulation of lenalidomide in plasma with multiple doses at 10 mg per day. Because many MDS patients have some degree of renal impairment, the exposure (AUC) is higher in MDS patients as compared with healthy subjects (dose adjustments are recommended for patients with CLcr < 60 mL/min; see section 4.2).

Distribution:

In vitro [^{14}C]-lenalidomide binding to plasma proteins is approximately 29 % in healthy volunteers and 23 % in multiple myeloma patients.

Lenalidomide is present in semen (< 0,01 % of the dose) after administration of 25 mg/day and the substance is undetectable in semen 3 days after discontinuation of lenalidomide.

Metabolism:

Lenalidomide is not a substrate of hepatic metabolic enzymes *in vitro*. Unchanged lenalidomide is the predominant circulation component *in vivo* in humans. Two identified metabolites are hydroxyl-lenalidomide and N-acetyl-lenalidomide; each constitute less than 5 % of parent levels in circulation.

Excretion:

Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy volunteers, approximately 90 % and 4 % of the radioactive dose is eliminated in urine and faeces, respectively. Approximately 82 % of the radioactive dose is excreted as lenalidomide, almost exclusively via the urinary route. Hydroxyl-lenalidomide and N-acetyl-lenalidomide represent 4,59 % and 1,83 % of the excreted dose, respectively. The renal clearance of lenalidomide exceeds glomerular filtration rate and therefore is at least actively secreted to some extent.

In MDS patients, urinary excretion of unchanged lenalidomide in 24 hours post-dose averages approximately 65 % of the administered dose. At recommended doses (5 to 25 mg/day), half-life in plasma is approximately 3 hours in healthy volunteers and ranged from 3 to 5 hours in patients with Multiple Myeloma or MDS.

Pharmacokinetics in children:

No data are available.

Pharmacokinetics in the elderly:

No data are available.

Pharmacokinetics in renal impairment:

The pharmacokinetics of lenalidomide are similar in patients with mild impairment CLcr 56-74 mL/min and healthy subjects. Moderately and severely impaired patients had a 3-fold increase in half-life and a 66 % to 75 % decrease in clearance compared to healthy subjects. Patients on haemodialysis had an approximately 4,5-fold increase in half-life and 80 % decrease in clearance compared to healthy subjects. Approximately 30 % of the substance in the body was removed by a 4-hour dialysis session.

Pharmacokinetics in hepatic impairment:

No data are available.

5.3 Preclinical safety data

Findings from an embryofoetal development study, administering lenalidomide at doses from 0,5 and up to 4 mg/kg/day in monkeys, indicate that lenalidomide produce external malformations including imperforate anus and malformations of upper and lower extremities (bent, shortened, malformed, malrotated and/or absent part of the extremities, oligo and/or polydactyly) in the offspring of female monkeys who receive the active substance during pregnancy.

Various visceral effects (discoloration, red foci at different organs, small colourless mass above atrio-ventricular valve, small gall bladder, malformed diaphragm) are observed in single foetuses.

Lenalidomide has a potential for acute toxicity; minimum lethal doses after oral administration are > 2000 mg/kg/day in rodents. Repeated oral administration of 75, 150 and 300 mg/kg/day to rats for up to 26 weeks produce a reversible treatment-related increase in kidney pelvis mineralisation in all 3 doses, most notably in females. The no observed adverse effect level (NOAEL) was considered to be less than 75 mg/kg/day,

and is approximately 25-fold greater than the human daily exposure based on AUC exposure. Repeated oral administration of 4 and 6 mg/kg/day to monkeys for up to 20 weeks produce mortality and significant toxicity (marked weight loss, reduced red and white blood cell and platelet counts, multiple organ haemorrhage, gastrointestinal tract inflammation, lymphoid, and bone marrow atrophy). Repeated oral administration of 1 and 2 mg/kg/day to monkeys for up to 1 year produce reversible changes in bone marrow cellularity, a slight decrease in myeloid/erythroid cell ratio and thymic atrophy. Mild suppression of white blood cell count is observed at 1 mg/kg/day corresponding to approximately the same human dose based on AUC comparisons.

In vitro (bacterial mutation, human lymphocytes, mouse lymphoma, Syrian Hamster Embryo cell transformation) and *in vivo* (rat micronucleus) mutagenicity studies reveal no drug related effects at either the gene or chromosomal level. Carcinogenicity studies with lenalidomide have not been conducted.

In developmental toxicity studies, rabbits were administered 3, 10 and 20 mg/kg/day orally. An absence of the intermediate lobe of the lung was observed at 10 and 20 mg/kg/day with dose dependence and displaced kidneys were observed at 20 mg/kg/day. Although it was observed at maternotoxic levels they may be attributable to a direct effect. Soft tissue and skeletal variations in the foetuses were also observed at 10 and 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Lactose anhydrous.

Capsule shell:

MYLOMID 2,5/ 5/ 7,5/ 10/ 15/ 25 mg:

Gelatine

Titanium dioxide (E171)

Black ink (contains: shellac (E904), black iron oxide (E172(i)), purified water)

MYLOMID 20 mg:

Gelatine

Titanium dioxide (E171)

FD&C Blue 1 (E133)

Iron oxide yellow (E172(iii))

FD&C Yellow 6 (E110)

Black ink (contains: shellac (E904), black iron oxide (E172(i)), purified water)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Do not remove capsule from blister until required for use.

6.5 Nature and contents of container

PVC/Aclar film with plain aluminium foil blisters containing 7 hard capsules per blister strip. The blisters are packed into cartons.

Pack size: 7, 14, 21 or 28.

6.6 Special precautions for disposal and other handling

MYLOMID capsules should not be opened, broken or chewed.

If powder from **MYLOMID** makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If **MYLOMID** makes contact with the mucous membranes, they should be thoroughly flushed with water.

Any unused product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Forrester Pharma (Pty) Ltd

13 Pasita Street

Rosen Heights

Rosen Park

Bellville

7530

South Africa

8. REGISTRATION NUMBERS

MYLOMID 2,5 mg: 54/32/0727.713

MYLOMID 5 mg: 54/32/0728.714

MYLOMID 7,5 mg: 54/32/0729.715

MYLOMID 10 mg: 54/32/0730.716

MYLOMID 15 mg: 54/32/0731.717

MYLOMID 20 mg: 54/32/0732.718

MYLOMID 25 mg: 54/32/0733.719

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Date of first authorisation: 06 October 2020