PROFESSIONAL INFORMATION FOR

EUROLEN 5 mg, 10 mg, 15 mg & 25 mg

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 in monkeys malformations similar to those described with thalidomide (see 'Pregnancy and lactation'). 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 EUROLEN AS NEGLIGIBLE AS POSSIBLE, IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME. THIS PROGRAMME IS CALLED THE EUROLAB PREGNANCY PROTECTION PROGRAMME.

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 EUROLAB PREGNANCY PROTECTION PROGRAMME.

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

EUROLEN 5 Hard capsules

EUROLEN 10 Hard capsules

EUROLEN 15 Hard capsules

EUROLEN 25 Hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **EUROLEN 5** hard capsule contains 5 mg of lenalidomide

Each **EUROLEN 10** hard capsule contains 10 mg of lenalidomide

Each **EUROLEN 15** hard capsule contains 15 mg of lenalidomide

Each **EUROLEN 25** hard capsule contains 25 mg of lenalidomide

The inactive ingredients include croscarmellose sodium, lactose, magnesium stearate and microcrystalline cellulose.

The 5 mg capsule shells contain FD&C Blue #1 (E133), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin.

The 10 mg capsule shells contain yellow iron oxide (E172), black iron oxide (E172), titanium dioxide (E171) and gelatin.

The 15 mg capsule shells contain black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin.

The 25 mg capsule shells contain titanium dioxide (E171) and gelatin.

Contains sugar (lactose).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

EUROLEN 5: A green opaque cap/ light brown opaque body, capsule shell size No. 2 imprinted in black ink with “LP” on the cap and “638” on the body and filled with white powder.

EUROLEN 10: A yellow opaque cap/ grey opaque body, capsule shell size No. 0 imprinted in black ink with “LP” on the cap and “639” on the body and filled with white powder.

EUROLEN 15: A brown opaque cap/ grey opaque body, capsule shell size No. 2 imprinted in black ink with “LP” on the cap and “640” on the body and filled with white powder.

EUROLEN 25: A white opaque cap/ white opaque body, capsule shell size No. 0 imprinted in black ink with “LP” on the cap and “642” on the body and filled with white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelodysplastic Syndromes (MDS):

EUROLEN 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:

EUROLEN 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

Myelodysplastic syndromes (MDS):

Recommended dosage:

The recommended starting dose of **EUROLEN** 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 **EUROLEN** treatment
Return to ≥ 50 x 10^9/l	Resume **EUROLEN** at 5 mg once a day continuously in repeating 28 day cycles
If baseline < 100 x 10^9/l	
When platelets	Recommend course
Fall to 50 % of the baseline value	Interrupt **EUROLEN** treatment
If baseline ≥ 60 x 10^9/l and returns to ≥ 50 x 10^9/l	Resume **EUROLEN** at 5 mg once a day continuously in repeating 28 day cycles
If baseline < 60 x 10^9/l and returns to ≥ 30 x 10^9/l	Resume **EUROLEN** 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 **EUROLEN** treatment
Return to ≥ 30 x 10^9/l (without signs of bleeding)	Resume **EUROLEN** 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	Interrupt **EUROLEN** treatment
With platelet transfusions	
Return to ≥ 30 x 10^9/l	Resume **EUROLEN** at 5 mg every other day
(without signs of bleeding)	

Neutrophils 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 **EUROLEN** treatment
Return to ≥ 1 x 10^9/l	Resume **EUROLEN** at 5 mg once a day continuously in repeating 28 day cycles

If baseline ANC < 1 x 10^9/l	
When Neutrophils	Recommend Course
Fall to < 0,5 x 10^9/l	Interrupt **EUROLEN** treatment
Return to ≥ 0,5 x 10^9/l	Resume **EUROLEN** 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 **EUROLEN** treatment
Return to ≥ 0,5 x 10^9/l	Resume **EUROLEN** 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
< 0,5x 10^9/l for ≥ 7 days or < 0,5 x 10^9/l associated with fever (≥ 38,5 °C)	Interrupt **EUROLEN** treatment
Return to ≥ 0,5 x 10^9/l	Resume **EUROLEN** 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 **EUROLEN**, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2 at the medical practitioner's discretion.

Discontinuation of EUROLEN

EUROLEN interruption or discontinuation should be considered for Grade 2-3 skin rash.

EUROLEN 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 **EUROLEN** 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 of 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 **EUROLEN**.

Platelet counts

Thrombocytopenia

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

Neutrophil counts (ANC)

Neutropenia

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

Other Grade 3/4 Toxicities

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

Discontinuation of EUROLEN

EUROLEN interruption or discontinuation should be considered for Grade 2-3 skin rash. **EUROLEN** 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 EUROLEN 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 **EUROLEN** treatment and follow CBC weekly	Starting dose	25 mg
Return to ≥ 30 x 10^9/l	Resume **EUROLEN** 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 **EUROLEN** treatment Resume **EUROLEN** at the next lower dose level -2 or -3 for the indicated dose regimen. Do not dose below the lowest **EUROLEN** dose level in the indicated dose regimen.	Dose Level -2	10 mg
		Dose Level -3	5 mg

Absolute neutrophil counts (ANC)

Neutropenia

When neutrophils	**Recommended course**	**Dose Level**	**Previously Treated Multiple Myeloma (combination with dexamethasone)**
			Days 1-21/28 day cycle

Fall to < 0,5 x 10^9/l	Interrupt **EUROLEN** treatment and follow CBC weekly	Starting Dose	25 mg
Return to ≥ 0,5 x 10^9/l	Resume **EUROLEN** at dose level -1	Dose Level-1	15 mg
For each subsequent drop below < 0,5 x 10^9/l Return to ≥ 0,5 x 10^9/l	Interrupt **EUROLEN** treatment Resume **EUROLEN** at the next lower dose level -2 or -3 for the indicated dose regimen.	Dose Level -2	10 mg
		Dose Level -3	5 mg
	Do not dose below the lowest **EUROLEN** dose level in the indicated dose regimen.		

a. At the medical practitioner'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 **EUROLEN**.

Other Grade 3/4 Toxicities

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

Discontinuation of EUROLEN

EUROLEN interruption or discontinuation should be considered for Grade 2-3 skin rash.

EUROLEN 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 for these reactions.

Paediatrics:

No data is 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 **EUROLEN** 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:

EUROLEN 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 **EUROLEN** 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	15 mg Every 48 hours	5 mg Every 48 hours

(CLcr < 30 ml/min, not requiring dialysis)		
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 patient is not responding to treatment and is tolerating the medicine.

After initiation of **EUROLEN** therapy, subsequent **EUROLEN** 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. **EUROLEN** is not known to be metabolised by the liver; the elimination of unchanged **EUROLEN** is predominantly by the renal route (see section 5.2).

Method of administration

EUROLEN should be taken orally at about the same time each day. The capsules should not be opened, broken, or chewed. **EUROLEN** 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 of **EUROLEN**.
- Pregnancy and lactation.
- Women of childbearing potential, except when all of the conditions for pregnancy prevention have been met (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

General:

Pregnancy warning

EUROLEN is contraindicated during pregnancy.

EUROLEN is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects (see section 4.6). If **EUROLEN** is taken during pregnancy, a teratogenic effect of lenalidomide is expected.

The conditions of the Eurolab Pregnancy Protection 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 to have childbearing potential unless she meets at least one of the following criteria:

- Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (Amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential).
- Premature ovarian failure confirmed by a specialist gynaecologist.
- Previous bilateral salpingo-oophorectomy, or hysterectomy.
- XY genotype, Turner syndrome, uterine agenesis.

Counselling

For women of childbearing potential, **EUROLEN** 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 including dose interruptions, and for 6 months 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 **EUROLEN** 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 **EUROLEN**.

For male patients taking **EUROLEN**, 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 healthy individuals (see section 5.2). As a precaution, all male patients taking **EUROLEN** must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with 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 3 months after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking **EUROLEN** or shortly after he has stopped taking **EUROLEN**, he should inform his treating 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 Eurolab Pregnancy Protection Programme, including confirmation that she has an adequate level of understanding.
- The patient has acknowledged the aforementioned conditions.

Contraception

Male patients treated with **EUROLEN** should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 3 months after exposure (i.e. five half-lives after the last dose, plus 60-75 days for sperm production plus 10-14 days for the transport to epididymis).

Women of childbearing potential must use two reliable methods of contraception for 4 weeks before therapy, during therapy including dose interruptions. Female patients and female sexual partners of male patients receiving **EUROLEN**, should be advised to avoid becoming pregnant and to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites plus an additional 6 months after exposure (i.e. five half-lives after the last dose, plus 6 months

which covers the growth and maturation phase of folliculogenesis), 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:
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 (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 **EUROLEN** and dexamethasone, and in patients with myelodysplastic syndromes, 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 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.

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.

Effective methods

- Male condom;
- Diaphragm;
- Cervical cap

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 **EUROLEN** 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 7 days prior to the patient starting **EUROLEN** 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 **EUROLEN**.

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 7 days prior to the visit to the prescriber.

Male fertility

EUROLEN is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after discontinuation of **EUROLEN.**

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 3 months 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 **EUROLEN** should not donate sperm or semen during treatment including dose interruptions and for 3 months following the end of treatment.

Patients should not donate blood during therapy including dose interruptions and for 4 weeks following discontinuation of **EUROLEN**.

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 for safe disposal.

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to **EUROLEN**, educational material will be provided to health care professionals to reinforce the warnings about the expected teratogenicity of **EUROLEN**, 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 Eurolab Pregnancy Protection Programme should be given by the medical practitioner 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 lenalidomide 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 lenalidomide, 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 minimize all modifiable risk factors (eg. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events (ATE)

Predominantly deep venous thrombosis and pulmonary embolism occurs in multiple myeloma patients treated with **EUROLEN** combination therapy and in MDS patients treated with **EUROLEN** monotherapy.

In patients with multiple myeloma, the combination of lenalidomide with dexamethasone is associated with an increased risk of arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event).

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimize 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 lenalidomide with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic medicines.

Patients and doctors 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 lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Pulmonary hypertension

Cases of pulmonary hypertension, some fatal, have been reported in patients treated with lenalidomide. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during lenalidomide therapy.

Allergic Conditions

Cases of allergic reaction/hypersensitivity reactions have been reported in patients treated with lenalidomide (see section 4.8).

Angioedema and serious dermatologic/ cutaneous reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of lenalidomide. These events can be fatal.

Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive **EUROLEN**, as a possible cross-reaction between lenalidomide and thalidomide has been reported in the literature. **EUROLEN** interruption or discontinuation of lenalidomide should be considered for Grade 2-3 skin rash, depending on severity. **EUROLEN** 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 for these reactions.

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.

Tumour Lysis Syndrome and Tumour Flare Reaction

Tumour lysis syndrome (TLS) and tumour flare reaction (TFR) have been observed in patients with CLL, and in patients with other lymphomas, who were treated with **EUROLEN**. Fatal instances of TLS have been reported during treatment with **EUROLEN**. 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 **EUROLEN**. 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 MM treated with **EUROLEN**.

Myelodysplastic syndromes (MDS):

The major dose limiting toxicities of lenalidomide include haematologic toxicity (neutropenia and thrombocytopenia) in deletion 5q MDS. 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 **EUROLEN** treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2).

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.

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

Multiple myeloma:

Haematological toxicities:

- Previously treated MM:

Haematologic toxicity (neutropenia and thrombocytopenia) in previously treated multiple myeloma patients treated with **EUROLEN** combination therapy – Complete blood cell counts should be monitored every 2 weeks for the first 12 weeks and then monthly thereafter. A dose interruption and/or dose reductions may be required (see section 4.2).

Second Primary Malignancies

- Previously treated MM

A numerical imbalance was observed in previously treated multiple myeloma patients with **EUROLEN** and dexamethasone compared with controls comprising invasive primary malignancies and of basal cell and squamous cell skin cancers.

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

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

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There is no increase in peripheral neuropathy observed with lenalidomide in combination with dexamethasone or lenalidomide monotherapy.

The combination of lenalidomide with intravenous dexamethasone in multiple myeloma patients is associated with a higher frequency of peripheral neuropathy. For additional information, see Section 4.8.

Hepatic disorders

Hepatic failure, including fatal cases, has been reported in patients treated with lenalidomide in combination therapy:

acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis have been reported. The mechanisms of severe medicine-induced hepatotoxicity remain 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 commonly reported and were generally asymptomatic and reversible upon dosing interruption. Once parameters have returned to baseline, treatment at a lower dose may be considered.

EUROLEN 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 lenalidomide is combined with medicinal products known to be associated with liver dysfunction.

Infection with or without neutropenia

Patients with multiple myeloma are prone to develop infections including pneumonia. A higher rate of infections is observed with lenalidomide in combination with dexamethasone. Infections occurs within the context of neutropenia in less than one-third of the patients. 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 (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

Viral reactivation

Cases of viral reactivation have been reported in patients receiving lenalidomide, 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 lenalidomide and adequate antiviral treatment.

Reactivation of hepatitis B has been reported in patients receiving lenalidomide 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 lenalidomide and adequate antiviral treatment. Hepatitis B virus status should be established before initiating treatment with lenalidomide. For patients who test positive for HBV infection, consultation with a medical practitioner with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when lenalidomide 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 lenalidomide. PML was reported several months to several years after starting the treatment with lenalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Doctors 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, **EUROLEN** must be permanently discontinued.

Cataract

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

Lactose intolerance

EUROLEN capsules contain lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **EUROLEN**.
Risk-benefit of **EUROLEN** treatment should be evaluated in patients with lactose intolerance.

4.5 Interactions with other medicines and other forms of interaction

In vitro studies demonstrate that **EUROLEN** 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 EUROLEN with dexamethasone (see sections 4.4 and 4.8).

Patients with multiple myeloma taking **EUROLEN** and dexamethasone, patients with MDS taking **EUROLEN** 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

Induction leading to reduced efficacy of medicines, including hormonal contraceptives, is not expected if **EUROLEN** 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).

Warfarin

Co-administration of multiple 10 mg doses of **EUROLEN** has no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of **EUROLEN**.

However, it is not known whether there is an interaction during clinical use (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 the treatment.

Digoxin

Concomitant administration with **EUROLEN** 10 mg once daily increases the plasma exposure of digoxin (0,5 mg, single dose) by 14 % with a 90 % CI (confidence interval) [0,52 % - 28,2 %]. It is not known whether the effect will be different in the clinical use (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during **EUROLEN** treatment.

Statins

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

Dexamethasone

In patients with multiple myeloma, co-administration of single or multiple doses of dexamethasone (40 mg once daily) has no clinically relevant effect on the multiple dose pharmacokinetics of **EUROLEN** (25 mg once daily).

Interactions with P-glycoprotein (P-gp) inhibitors

In vitro, **EUROLEN** is a weak substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600 mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25 mg) has no clinically relevant effect on the pharmacokinetics of **EUROLEN** (25 mg). Co-administration of **EUROLEN** does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation

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

Women of childbearing potential/ Contraception in males and females

Males:

EUROLEN is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after stopping lenalidomide. As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking **EUROLEN** should use condoms throughout treatment duration, during dose interruption and for 3 months after cessation of treatment if their partner is pregnant or of childbearing potential and has no contraception.

Males using **EUROLEN** should not donate sperm or semen during treatment including dose interruptions and for 3 months following the discontinuation of treatment.

Criteria for women of non-childbearing potential

Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with **EUROLEN**, treatment must be stopped and the patient

should be referred to a doctor specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking **EUROLEN**, it is recommended to refer the female partner to a medical practitioner specialised or experienced in teratology for evaluation and advice.

A female patient or a 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 does not rule out childbearing potential.

Pregnancy

EUROLEN is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. Therefore:

- Females of childbearing potential must use effective means of contraception for 28 days before therapy, during **EUROLEN** therapy including dose interruptions, and for 6 months following discontinuation of **EUROLEN** therapy, or continually abstain from sexual intercourse. There is an increased risk of VTE in patients with multiple myeloma taking **EUROLEN** and dexamethasone, and in patients with MDS taking **EUROLEN** 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 **EUROLEN**.
- If pregnancy does occur during treatment, **EUROLEN** should be immediately discontinued.

Teratogenic effects of lenalidomide is expected, therefore **EUROLEN** is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is not known whether lenalidomide is excreted in breast milk. Therefore, breastfeeding is contraindicated during therapy with **EUROLEN**.

Fertility

EUROLEN has no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines

EUROLEN can influence the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of **EUROLEN**. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

a. Summary of the safety profile

Multiple myeloma: patients with at least one prior therapy

The most serious adverse reactions observed more frequently with lenalidomide and dexamethasone combination therapy:

• Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)

• Grade 4 neutropenia (see section 4.4).

Myelodysplastic syndromes

Serious adverse reactions include:

• Venous thromboembolism (deep vein thrombosis, pulmonary embolism) (see section 4.4)

• Grade 3 or 4 neutropenia, febrile neutropenia and grade 3 or 4 thrombocytopenia (see section 4.4).

Teratogenicity

Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. If **EUROLEN** is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

Venous thromboembolism

An increased risk of DVT and PE (deep vein thrombosis, pulmonary embolism) is associated with the use of the combination of lenalidomide with dexamethasone in patients with multiple myeloma.

Concomitant administration of erythropoietic medicines or previous history of DVT may also increase thrombotic risk in these patients.

Myocardial infarction

Myocardial infarction has been reported in patients receiving lenalidomide, particularly in those with known risk factors.

Allergic reactions

Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide and thalidomide has been reported.

Severe skin reactions

Severe cutaneous reactions including SJS and TEN have been reported with the use of lenalidomide. Patients with a history of severe rash associated with thalidomide treatment should not receive lenalidomide (see section 4.4).

Hepatic disorders

The following adverse reactions have been reported (frequency unknown): acute hepatic failure and cholestasis (both potentially fatal), toxic hepatitis, cytolytic hepatitis, mixed cytolytic/cholestatic hepatitis.

Rhabdomyolysis

Rare cases of rhabdomyolysis have been observed, some of them when lenalidomide is administered with a statin.

Gastrointestinal disorders

Gastrointestinal perforations have been reported during treatment with lenalidomide. Gastrointestinal perforations may lead to septic complications and may be associated with fatal outcome.

b. Tabulated summary of adverse reactions

The following side effects to be considered in patients with Relapsed and Refractory Multiple Myeloma and Myelodysplastic Syndromes, treated with **EUROLEN**:

Infections and Infestations

Frequent:	Pneumonia, bronchitis, bacterial, viral and fungal infections (including opportunistic infections), upper respiratory tract infection, sinusitis
Frequency unknown:	Viral infections, including herpes zoster and hepatitis B virus reactivation

Neoplasms benign and malignant (including cysts and polyps)

Frequent:	B-cell lymphomas
Less frequent:	Tumour lysis syndrome
Frequency unknown:	Tumour flare reaction (TFR)

Blood and lymphatic system disorders

Frequent:	Neutropenia, thrombocytopenia, anaemia, leukopenia, febrile neutropenia
Frequency unknown:	Acquired haemophilia

Immune system disorders

Less frequent:	Hypersensitivity (also a possibility of cross-reaction with thalidomide)
Frequency unknown:	Solid organ transplant rejection, anaphylactic reaction

Endocrine disorders

Frequent:	Hypothyroidism, hyperthyroidism

Metabolism and nutrition disorders

Frequent:	Decreased appetite, hypokalaemia, hypocalcaemia, dehydration, dypomagnesaemia, iron overload, hypophosphataemia, hyperglycaemia, weight decreased
Frequency unknown:	Tumour Lysis syndrome (TLS)

Psychiatric disorders

Frequent:	Depression, altered mood

Nervous system disorders

Frequent:	Peripheral neuropathies (excluding motor neuropathy), dizziness, tremor, dysguesia, headache, lethargy, paraesthesia, syncope, cerebrovascular accident

Eye disorders

Frequent:	Blurred vision, cataracts

Cardiac disorders

Frequent:	Acute myocardial infarction, atrial fibrillation, tachycardia, cardiac failure congestive, cardiac failure

Vascular disorders

Frequent:	Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism (especially in combination therapy with dexamethasone and other erythropoietic medicines), hypertension, hypotension, haematoma

Respiratory, thoracic and mediastinal disorders

Frequent:	Dyspnoea, epistaxis, respiratory distress, bronchitis
Frequency unknown:	Interstitial pneumonitis, pulmonary hypertension

Gastrointestinal disorders

Frequent:	Diarrhoea, vomiting, nausea, constipation, abdominal Pain (including upper), dry mouth, dyspepsia, toothache
Frequency unknown:	Pancreatitis, gastrointestinal perforation (including diverticular, intestinal and large intestine perforations)

Hepato-biliary disorders

Frequent:	Abnormal liver function tests
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
Less frequent:	Angioedema, Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN)
Frequency unknown:	Leukocytoclastic vasculitis, medicine reaction with eosinophilia and systemic symptoms, Second primary malignancies (mainly basal cell or squamous cell skin cancers)

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, muscular weakness, back pain
Less frequent:	Rhabdomyolysis, sometimes in combination with a statin

Renal and urinary disorders

Frequent:	Renal failure

Pregnancy, puerperium and perinatal conditions

Frequency unknown:	Teratogenic (causes severe life-threatening birth defects)

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

Investigations

Frequent: Decreased weight

Injury, poisoning and procedural complications

Frequent: Fall

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (whoumc.org) found on SAHPRA website or to Eurolab (Pty) Ltd. by email: drug-safety@eurolab.co.za.

4.9 Overdose

There is no specific experience in the management of **EUROLEN** overdose in patients.

In studies, the dose-limiting toxicity was essentially haematological. In the event of overdose, supportive care is advised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A32 Other - Immunomodulators.

Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

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 which have reduced expression due to haploinsufficiency caused by del (5q).

Cardiac Electrophysiology

A single dose of lenalidomide up to 50 mg is not associated with prolongation of the QT interval in healthy males.

5.2 Pharmacokinetic properties

Absorption

Lenalidomide 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 a high-fat and high-calorie meal, 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 previous studies, lenalidomide 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 individuals, since lenalidomide clearance is lower in these patients than in healthy individuals. 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 and "**Use in Patients with Impaired Renal Function**").

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 individuals (dose adjustments are recommended for patients with CLcr < 60 ml/min; see section 4.2 and "**Use in Patients with Impaired Renal Function**").

Distribution

In vitro [^{14}C]-lenalidomide binding to plasma proteins is approximately 29 % in healthy individuals 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 circulating component *in vivo* in humans. Two identified metabolites are hydroxy-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 individuals, 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. Hydroxy-lenalidomide and N-acetyl-lenalidomide represent 4,59 % and 1,83 % of the excreted dose, respectively. The renal clearance of lenalidomide exceeds the 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 individuals and ranges from 3 to 5 hours in patients with multiple myeloma or MDS.

Special populations:

Adolescents

No data is available.

Elderly

No data is available.

Renal impairment

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

Hepatic Impairment

No data is available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients include croscarmellose sodium, lactose, magnesium stearate and microcrystalline cellulose.

The 5 mg capsule shells contain FD&C Blue #1 (E133), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin.

The 10 mg capsule shells contain yellow iron oxide (E172), black iron oxide (E172), titanium dioxide (E171) and gelatin.

The 15 mg capsule shells contain black iron oxide (E172), red iron oxide (E172), yellow iron oxide (E172), titanium dioxide (E171) and gelatin.

The 25 mg capsule shells contain titanium dioxide (E171) and gelatin.

Printing ink contains Shellac (E904), propylene glycol (E1520), strong ammonia solution (E527), black iron oxide (E172) and potassium hydroxide (E525).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C. Keep in the original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

EUROLEN is packed in PVC/ACLAR/Aluminium blister packs packed in an outer carton. Each pack of **EUROLEN** contains 3 blister strips of 7 capsules each (Total of 21 capsules per pack).

6.6 Special precautions for disposal and other handling

Capsules should not be opened or crushed. If powder from **EUROLEN** makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If **EUROLEN** 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

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBERS

EUROLEN 5: A53/32/0739

EUROLEN 10: A53/32/0740

EUROLEN 15: A53/32/0741

EUROLEN 25: A53/32/0742

9 DATE OF FIRST AUTHORISATION

29 September 2020

10 DATE OF REVISION OF TEXT

06 November 2024

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable