Module 1.3.1.1: Professional Information for

LENALIDOMIDE CIPLA 5, 10, 15, 25 (Capsules)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LENALIDOMIDE CIPLA 5 hard gelatin capsules

LENALIDOMIDE CIPLA 10 hard gelatin capsules

LENALIDOMIDE CIPLA 15 hard gelatin capsules

LENALIDOMIDE CIPLA 25 hard gelatin capsules

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 **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 LENALIDOMIDE CIPLA AS NEGLIGABLE AS POSSIBLE, LENALIDOMIDE CIPLA IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION RISK MANAGEMENT PROGRAMME.

UNDER THE RESTRICTED DISTRIBUTION RISK MANAGEMENT PROGRAMME, ONLY PRESCRIBERS REGISTERED WITH THE PROGRAMME ARE ALLOWED TO PRESCRIBE THE PRODUCT AND PHARMACISTS REGISTRED WITH THE PROGRAMME ARE

ALLOWED TO DISPENSE THE PRODUCT. IN ADDITION, PATIENTS MUST BE ADVISED OF, AGREE TO, AND COMPLY WITH THE REQUREMENTS OF RESTRICTED DISTRIBUTION RISK MANAGEMENT PROGRAM.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **LENALIDOMIDE CIPLA 5** hard gelatin capsule contains 5 mg of lenalidomide.

Each **LENALIDOMIDE CIPLA 10** hard gelatin capsule contains 10 mg of lenalidomide.

Each **LENALIDOMIDE CIPLA 15** hard gelatin capsule contains 15 mg of lenalidomide.

Each **LENALIDOMIDE CIPLA 25** hard gelatin capsule contains 25 mg of lenalidomide.

For full list of excipients, see **section 6.1**

Contains sugar (147 mg anhydrous lactose for lenalidomide 5 mg)

Contains sugar (294 mg anhydrous lactose for lenalidomide 10 mg)

Contains sugar (120 mg anhydrous lactose for lenalidomide 15 mg)

Contains sugar (200 mg anhydrous lactose for lenalidomide 25 mg).

3. PHARMACEUTICAL FORM

LENALIDOMIDE CIPLA 5 hard gelatin capsules: White to off white powder filled in size ‘2’ hard gelatin white and white capsule spin printed in black ink with ‘Cipla 5 mg’ on the cap.

LENALIDOMIDE CIPLA 10 hard gelatin capsules: White to off white powder filled in size ‘0’ hard gelatin blue green and pale-yellow capsule spin printed in black ink with ‘Cipla 10 mg’ on the cap.

LENALIDOMIDE CIPLA 15 hard gelatin capsules: White to off white powder filled in size ‘0’ hard gelatin pale blue and white capsule spin printed in black ink with ‘Cipla 15 mg’ on the cap.

LENALIDOMIDE CIPLA 25 hard gelatin capsules: White to off white powder filled in size ‘0’ hard gelatin white and white capsule spin printed in black ink with ‘Cipla 25 mg’ on the cap.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

LENALIDOMIDE CIPLA is indicated for the following:

- ***Myelodysplastic Syndromes (MDS)***

LENALIDOMIDE CIPLA 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 (MM)***

LENALIDOMIDE CIPLA 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

Treatment with LENALIDOMIDE CIPLA should be supervised by a medical practitioner experienced in the use of anti-cancer therapies.

Posology

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

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.

Myelodysplastic syndromes (MDS)

Recommended dosage

The recommended starting dose of LENALIDOMIDE CIPLA 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 × 10^9/L	
When Platelets	Recommended Course
Fall to < 50 × 10^9/L	Interrupt LENALIDOMIDE CIPLA treatment
Return to ≥ 50 × 10^9/L	Resume LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA treatment
If baseline ≥ 60 x 10^9/ L and returns to ≥ 50 x 10^9/ L	Resume LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA 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 × 10^9/L or < 50 × 10^9/L with platelet transfusions	Interrupt LENALIDOMIDE CIPLA treatment
Return to ≥ 30 x 10^9/L (without signs of bleeding)	Resume LENALIDOMIDE CIPLA 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 1 0^9/L or < 50 x 1 0^9/L with platelet transfusions	Interrupt LENALIDOMIDE CIPLA treatment
Return to ≥ 30 x 10^9/L (without signs of bleeding)	Resume LENALIDOMIDE CIPLA 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 × 10^9/L	
When Neutrophils	Recommended Course
Fall to < 0,75 × 10^9/L	Interrupt LENALIDOMIDE CIPLA treatment
Return to ≥ 1 × 10^9/L	Resume LENALIDOMIDE CIPLA at 5 mg once a day continuously in repeating 28-day cycles

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

Discontinuation of LENALIDOMIDE CIPLA

LENALIDOMIDE CIPLA interruption or discontinuation should be considered for Grade 2 – 3 skin rash. LENALIDOMIDE CIPLA must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (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 LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA.

Platelet counts

Thrombocytopenia

See table below entitled, 'Dose Reduction Steps for LENALIDOMIDE CIPLA in Previously Treated Multiple Myeloma'

Neutrophil counts (ANC)

Neutropenia

See table below entitled, 'Dose Reduction Steps for LENALIDOMIDE CIPLA in Previously Treated Multiple Myeloma'

Other Grade 3/4 Toxicities

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

Discontinuation of LENALIDOMIDE CIPLA

LENALIDOMIDE CIPLA interruption or discontinuation should be considered for Grade 2-3 skin rash. LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA in Previously Treated Multiple Myeloma

Platelet counts

Thrombocytopenia

			Previously Treated Multiple Myeloma (combination with dexamethasone)
			Days 1-21/28-day cycle
When platelets	**Recommended Course**	**Dose Levels**	
Fall to < 30 × 10^9/L	Interrupt LENALIDOMIDE CIPLA treatment and follow CBC weekly	Starting Dose	25 mg
Return to ≥ 30 × 10^9/L	Resume LENALIDOMIDE CIPLA at dose level - 1	Dose level – 1	15 mg
For each		Dose level – 2	10 mg

subsequent drop below < 30 × 10^9/L Return to ≥ 30 × 10^9/L	Interrupt LENALIDOMIDE CIPLA treatment Resume LENALIDOMIDE CIPLA at the next lower dose level -2 or -3 for the Indicated dose regimen. Do not dose below the lowest LENALIDOMIDE CIPLA dose level in the indicated dose regimen.	Dose level – 3	5 mg

Absolute neutrophil counts (ANC) Neutropenia

			Previously Treated Multiple Myeloma (combination with dexamethasone)
			Days 1 – 21/28 day cycle

When neutrophils	**Recommended Course[a]**	**Dose Levels**	
Fall to < 0,5 × 10^9/L	Interrupt LENALIDOMIDE CIPLA treatment and follow CBC weekly	Starting Dose	25 mg
Return to ≥ 0,5 × 10^9/L	Resume LENALIDOMIDE CIPLA at dose level - 1	Dose level – 1	15 mg
For each subsequent drop below < 0,5 × 10^9/L Return to ≥ 0,5 × 10^9/L	Interrupt LENALIDOMIDE CIPLA treatment Resume LENALIDOMIDE CIPLA at the next lower dose level -2 or -3 for the Indicated dose regimen. Do not dose below the lowest LENALIDOMIDE CIPLA dose level in the indicated dose regimen.	Dose level – 2	10 mg
		Dose level – 3	5 mg

[a]At the medical practitioner's descretion, If neutropenia IS the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of LENALIDOMIDE CIPLA.

Other Grade 3/4 Toxicities

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

Discontinuation of LENALIDOMIDE CIPLA

LENALIDOMIDE CIPLA interruption or discontinuation should be considered for Grade 2–3 skin rash. LENALIDOMIDE CIPLA 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.

SPECIAL POPULATIONS

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 LENALIDOMIDE CIPLA 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

LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA 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 patient is not responding to treatment and is tolerating the medicine.

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

Method of administration

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

4.3. Contraindications

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

4.4. Special warnings and precautions for use

General

Pregnancy warning

LENALIDOMIDE CIPLA is contraindicated during pregnancy.

LENALIDOMIDE CIPLA is structurally related to thalidomide. Thalidomide is 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 **section 4.6**).

If LENALIDOMIDE CIPLA is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of the 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, LENALIDOMIDE CIPLA 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, 4 weeks before starting treatment, throughout the entire duration of treatment including dose interruptions, and 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 LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA.

For male patients taking LENALIDOMIDE CIPLA, 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 subjects (see **section 5.2**). As a precaution, all male patients taking LENALIDOMIDE CIPLA 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 woman of childbearing potential.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the 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 4 weeks before therapy, during therapy including dose interruptions, and until 4 weeks after LENALIDOMIDE CIPLA 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 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.

Effective methods

- Male condom;
- Diaphragm;

- Cervical cap.

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking LENALIDOMIDE CIPLA and dexamethasone, and in patients with myelodysplastic syndromes taking LENALIDOMIDE CIPLA monotherapy, 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.

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 LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA.

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

LENALIDOMIDE CIPLA is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after discontinuation of LENALIDOMIDE CIPLA in the healthy subjects (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 LENALIDOMIDE CIPLA should not donate sperm or semen during treatment including dose interruptions and for 4 weeks following the end of treatment.

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

Educational materials

In order to assist patients in avoiding foetal exposure to LENALIDOMIDE CIPLA, educational material will be provided to health care professionals to reinforce the warnings about the expected teratogenicity of LENALIDOMIDE CIPLA, 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 Risk Management Program should be given by the medical practitioner to women of childbearing potential and, as appropriate, to male patients.

Other special warnings and precautions for use:

- *Myocardial infarction*

  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 (e.g. smoking, hypertension, and hyperlipidaemia).

- *Venous thromboembolic events*

  Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism), in multiple myeloma patients treated with LENALIDOMIDE CIPLA combination therapy and in MDS patients treated with LENALIDOMIDE CIPLA monotherapy.

  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.

  Patients and medical practitioners 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, as in LENALIDOMIDE CIPLA. Patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease prior to initiating and during LENALIDOMIDE CIPLA therapy.

- *Allergic Conditions*

  Angioedema and serious dermatologic reactions including (SJS) and (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive LENALIDOMIDE CIPLA. LENALIDOMIDE CIPLA interruption or discontinuation should be considered for Grade 2 – 3 skin rash. LENALIDOMIDE CIPLA 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.

- *Tumour Lysis Syndrome and Tumour Flare Reaction*

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

Myelodysplastic syndromes (MDS)

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A complete blood cell count, including white blood cell count with differential, platelet count, haemoglobin, and haematocrit should be performed at baseline, weekly for first 8 weeks of LENALIDOMIDE CIPLA treatment and monthly thereafter to monitor for cytopenia's. A dose reduction may be required **(see, section 4.2).**

In mantle cell lymphoma patients, the monitoring scheme should be every 2 weeks in Cycles 3 and 4, and then at the start of each cycle. A dose reduction may be required.

In case of neutropenia, the medical practitioners should consider the use of growth factors in patient management. Patients should be advised to promptly report febrile episodes.

Patients and medical practitioners 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 lenalidomide 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 LENALIDOMIDE CIPLA combination therapy- Complete blood cell counts should be monitored every 2 weeks for the first 12 weeks and then monthly thereafter. Some dose interruption and/or dose reductions may be required (see **section 4.2**).

Second Primary Malignancies

- Previously treated MM

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

Peripheral neuropathy

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy.

There is increase in peripheral neuropathy observed with lenalidomide in combination with dexamethasone or melphalan and prednisone or lenalidomide monotherapy or with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma.

The combination of lenalidomide with intravenous bortezomib and dexamethasone in multiple myeloma patients is associated with a higher frequency of peripheral neuropathy. The frequency was lower when bortezomib was administered subcutaneously (see **section 4.8**).

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

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 drug-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.

Renal disorder

Lenalidomide 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 medicines known to be associated with liver dysfunction.

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.

Paediatrics

LENALIDOMIDE CIPLA should not be used in children and adolescents from birth to less than18 years because of safety concerns

Lactose intolerance: LENALIDOMIDE CIPLA capsules contain lactose, which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take LENALIDOMIDE CIPLA.

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 LENALIDOMIDE CIPLA is not likely to result in clinically relevant medicine interactions.

Co-administration of multiple doses of 10 mg of LENALIDOMIDE CIPLA had no effect on the single dose pharmacokinetics and pharmacodynamic of R-and S-warfarin. Co-administration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of LENALIDOMIDE CIPLA. 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.

When digoxin is co-administered with LENALIDOMIDE CIPLA (10 mg/day) the digoxin C_{max} and $AUC0_{-\infty}$ is 14 % higher than when digoxin was administered concomitantly with placebo. Periodic monitoring of digoxin plasma levels is recommended during administration of LENALIDOMIDE CIPLA.

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 LENALIDOMIDE CIPLA (25 mg/day).

In vitro, indicates that LENALIDOMIDE CIPLA is a weak substrate, but is not an inhibitor of P-glycoprotein (P-gp). It demonstrates that LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA with dexamethasone (see **section 4.4 and 4.8**).

Patients with multiple myeloma taking LENALIDOMIDE CIPLA and dexamethasone, patients with MDS taking LENALIDOMIDE CIPLA monotherapy, as well as patients taking combined oral

contraceptive pills or hormone replacement therapy, have an increased risk of venous thromboembolic events (VTE).

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.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females

LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA therapy including dose interruptions, and for 28 days following discontinuation of LENALIDOMIDE CIPLA therapy, or continually abstain from sexual intercourse. There is an increased risk of VTE in patients with multiple myeloma taking LENALIDOMIDE CIPLA and dexamethasone, and in patients with MDS taking LENALIDOMIDE CIPLA 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 LENALIDOMIDE CIPLA.
- If pregnancy does occur during treatment, LENALIDOMIDE CIPLA should be immediately discontinued.

Males

- Lenalidomide is present in human semen. Therefore, male patients taking LENALIDOMIDE CIPLA should use a condom during LENALIDOMIDE CIPLA therapy including dose interruptions and for 4 weeks after cessation of treatment. Male patients taking LENALIDOMIDE CIPLA 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 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

LENALIDOMIDE CIPLA is contraindicated in females who are pregnant or who could become pregnant.

Breast-feeding

Breastfeeding is contra-indicated during therapy with LENALIDOMIDE CIPLA

4.7. Effects on ability to drive and use machines

LENALIDOMIDE CIPLA may affect the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of LENALIDOMIDE CIPLA. Therefore, caution is recommended when driving or operating machines.

4.8. Undesirable effects

a) Summary of the safety profile

Overall reported Adverse Drug Reactions (ADR's) in Relapsed and Refractory Multiple Myeloma and Myelodysplastic Syndromes:

Adverse reactions observed in patients are listed below by system organ class and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

b) Tabulated list of adverse reactions

MedDRA system organ classes (SOC)	Frequency of side effects	All Side effects	Grade 3/4 Side effects	SADRs
Infections and Infestations	Frequent	Pneumonia, bronchitis, bacterial, viral, and fungal infections (including opportunistic infections), upper respiratory tract infection, sinusitis, neutropenic infection, rhinitis, nasopharyngitis, influenza, gastroenteritis, lung	Pneumonia, bacterial, viral, and fungal infections (including opportunistic infections)	Pneumonia, bacterial, viral, and fungal infections (including opportunistic infections)

		infection, urinry tract infection and lower resp tract infection, and sepsis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequent	Myelodysplastic syndrome, basal cell carcinoma and squamous skin cancer		B-cell lymphomas
Blood and the lymphatic systems disorders	Frequent	Neutropenia, thrombocytopenia, anaemia, leukopenia	Neutropenia, thrombocytopenia, anaemia, leukopenia, febrile neutropenia	Neutropenia, thrombocytopenia, anaemia, febrile neutropenia lymphopenia, pancytopenia
	Less Frequent	haemolysis, autoimmune haemolytic anaemia and haemolytic anaemia		
Immune system disorders	Less Frequent	Hypersensitivity		
Endocrine disorder	Frequent	Hypothyroidism		
Metabolism and nutrition disorders	Frequent	Decreased appetite, hypokalaemia, hypocalcaemia, dehydration, hypomagnesaemia,	Hypokalaemia, hypocalcaemia, hypophosphataemia, hyperglycaemia, decreased appetite	Hyperglycaemia

		iron overload, hyperuricaemia		
Psychiatric disorders	Frequent		Depression	Altered mood
	Less Frequent	Insomnia, loss of libido		
Nervous system disorders	Frequent	Peripheral neuropathies (excluding motor neuropathy), dizziness, tremor, dysgeusia, headache, paraesthesia, lethargy	Syncope, dizziness	Cerebrovascular accident
Eye disorders	Frequent	Blurred vision, reduced visual acuity	Cataracts	
Ear and Labyrinth disorders	Frequent	Vertigo		
Cardiac disorders	Frequent		Acute myocardial infarction, atrial fibrillation, tachycardia, cardiac failure congestive, cardiac failure	Acute myocardial infarction, atrial fibrillation, cardiac failure congestive, cardiac failure
	Less Frequent	dysrhythmia, QT prolongation, atrial flutter, ventricular extrasystoles		
Vascular disorders	Frequent	Venous thromboembolic events,	Venous thromboembolic events,	Venous thromboembolic events,

		predominantly deep vein thrombosis, pulmonary embolism, hypertension, hypotension, haematoma	predominantly deep vein thrombosis and pulmonary embolism	predominantly deep vein thrombosis and pulmonary embolism
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, epistaxis, cough, rhinorrhoea, ecchymosis	Respiratory distress, bronchitis, pulmonary hypertension	
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, nausea, constipation, abdominal pain (including upper), dry mouth, dyspepsia, stomatitis, dysphagia, GI haemorrhage	Diarrhoea, nausea, constipation, toothache	Diarrhoea
	Less Frequent	Colitis, caectiis		
Hepato-biliary disorders	Frequent	Abnormal liver function tests	Abnormal liver function tests	Abnormal liver function tests
	Less Frequent	Hepatic failure		
Skin and subcutaneous tissue disorders	Frequent	Rash, pruritus, dry skin, eczema, erythema, hyperpigmentation	Rash, pruritus	

		and urticaria hyperhidrosis,		
	Less Frequent	skin discoloration, photosensitivity reaction		
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, joint swelling	Muscular weakness, musculoskeletal and connective tissue pain and discomfort (including back pain and pain in extremity),	Back pain
Renal and urinary disorders	Frequent	urinary retention, urinary incontinence	Renal failure	Renal failure
	Less Frequent	Acquired fanconis syndrome		
General disorders and administration site conditions	Frequent	Pyrexia, oedema (including peripheral oedema), influenza like illness syndrome (including pyrexia, cough, myalgia, musculoskeletal pain, headache, and rigors), fatigue,	Fatigue, pyrexia, asthenia, fall	

		asthenia, chest pain, lethargy		
Reproductive System and Breast Disorders	Frequent	Erectile dysfunction		
Investigations	Frequent	Decreased weight		
Injury, Poisoning and Procedural Complications		Fall, contusion		

Hepatic Disorders

Transient liver laboratory abnormalities (predominantly transaminases) were reported in patients treated with LENALIDOMIDE CIPLA. Treatment with LENALIDOMIDE CIPLA 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.

Post-marketing

MedDRA system organ classes (SOC)	**Frequency of side effects**	**All Side effects**	**Grade 3/4 Side effects**
Respiratory, thoracic and mediastinal disorders	Unknown	Pulmonary hypertension	Pulmonary hypertension, interstitial pneumonitis

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. 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 or drugsafetysa@cipla.com

4.9. Overdose

There is no specific experience in the management of LENALIDOMIDE CIPLA overdose in patients. In the event of overdose, supportive care is advised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: A 32 Other – Immunomodulators

Lenalidomide is an oral immunomodulating medicine with a pleiotropic mechanism of action 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 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, is rapidly absorbed following oral administration, reaching peak plasma levels within 0,5 and 1,5 hours. 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. 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 patients since lenalidomide clearance is lower in these patients than in healthy. 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 'dosage and directions for use' 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 subjects (dose adjustments are recommended for patients with CLcr < 60 mL/min; see 'dosage and directions for use' and 'use in patients with impaired renal function').

Distribution

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.

Biotransformation

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.

Elimination

A single oral administration of [^{14}C]-Lenalidomide (25 mg) to healthy patients, 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 lenalidmoide in 24 hours post-dose average 65 % of administered dose.

Pharmacokinetics in children

No data are available.

Pharmacokinetics in the elderly

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and would be prudent to monitor renal function.

Pharmacokinetics in renal Impairment

The pharmacokinetics of lenalidomide are similar in patients with mild impairment CLcr 56 – 74 mL/min and healthy subjects. Patients on haemodialysis could have an approximately 4,5-fold increase in half-life and an 80 % decrease in clearance compared to healthy subjects. Patients with renal dysfunction receiving the standard dose are particularly prone to developing hepatoxicity and renal dysfunction. In CCL patients, lenalidomide causes dramatic lymph node swelling and tumour lysis, a syndrome called the tumour flare reaction.

Pharmacokinetics in hepatic impairment

There are no data available for patients with moderate to severe hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Anhydrous lactose (Duralac H)

Croscarmellose sodium (AC-DI-SOL)

Magnesium stearate (vegetable grade)

Microcrystalline cellulose (Avicel PH 102)

Hard gelatin capsule: The composition of empty hard gelatin capsule are:

Gelatin

Titanium dioxide (E171)

Yellow iron oxide (E172) for 10 mg ONLY

Indigotine FD&C Blue #2 (E132) for 10 mg & 15 mg ONLY

Composition of ink used for printing on Capsule Shella are:

Shellac - E904

Propylene glycol – E1520

Strong amonia solution – E527

Black iron oxide – E172

Potassium hydroxide – E525

6.2. Incompatibilities

Not applicable

6.3 Shelf Life

36 months, stored at or below 25 °C

6.4 Special precautions for storage

Store at or below 25 °C. Keep in the outer carton until required for use.

6.5. Nature and contents of container

LENALIDOMIDE CIPLA 5**,** is supplied in a 0,025/190 mm Blister foil having 6-8 GSM UHSL with NC coating & 0,25/194 mm PVC/Aclar film with 51-micron Aclar clear.

Each blister pack contains 7 capsules. Each carton contains either a single blister pack (7’s pack size) or three blister packs (21’s pack size).

LENALIDOMIDE CIPLA 10; 15 & 25 are supplied in a 0,025/150 mm Blister foil having 6-8 GSM UHSL with NC coating & 0,25/154 mm PVC/Aclar film with 51-micron Aclar clear.

Each blister pack contains 7 capsules. Each carton contains either a single blister pack (7's pack size) or three blister packs (21's pack size).

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements**.**

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

LENALIDOMIDE CIPLA 5: 55/32/0295.294

LENALIDOMIDE CIPLA 10: 53/32/0374.371

LENALIDOMIDE CIPLA 15: 53/32/0375.372

LENALIDOMIDE CIPLA 25: 53/32/0376.373

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 July 2020

Date of latest renewal: N/A

10. DATE OF REVISION OF THE TEXT

18 March 2021