SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
NEOLED® 2,5 mg (Hard gelatine capsules)
NEOLED® 5 mg (Hard gelatine capsules)
NEOLED® 7,5 mg (Hard gelatine capsules)
NEOLED® 10 mg (Hard gelatine capsules)
NEOLED® 15 mg (Hard gelatine capsules)
NEOLED® 20 mg (Hard gelatine capsules)
NEOLED® 25 mg (Hard gelatine capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
NEOLED 2,5 mg: Each hard gelatine capsule contains 2,5 mg of lenalidomide.
Excipient(s) with known effect: Each capsule contains 33,2 mg of lactose.
NEOLED 5 mg: Each hard gelatine capsule contains 5 mg of lenalidomide.
Excipient(s) with known effect: Each capsule contains 66,4 mg of lactose.
NEOLED 7,5 mg: Each hard gelatine capsule contains 7,5 mg of lenalidomide.
Excipient(s) with known effect: Each capsule contains 99,7 mg of lactose.
NEOLED 10 mg: Each hard gelatine capsule contains 10 mg of lenalidomide.
Excipient(s) with known effect: Each capsule contains 132,9 mg of lactose.
NEOLED 15 mg: Each hard gelatine capsule contains 15 mg of lenalidomide.
Excipient(s) with known effect: Each capsule contains 199,3 mg of lactose.
NEOLED 20 mg: Each hard gelatine capsule contains 20 mg of lenalidomide.
Excipient(s) with known effect: Each capsule contains 265,8 mg of lactose.
NEOLED 25 mg: Each hard gelatine capsule contains 25 mg of lenalidomide.
Excipient(s) with known effect: Each capsule contains 332,2 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard gelatine capsules.

NEOLED 2,5 mg (hard gelatine capsules)
Hard gelatine capsule, with an opaque white body and opaque green cap with “L9NL” and “2.5” printed radial on body. Capsule size: 4
NEOLED 5 mg (hard gelatine capsules)
Hard gelatine capsule, with an opaque white body and opaque white cap with “L9NL” and “5” printed radial on body. Capsule size: 2
NEOLED 7,5 mg (hard gelatine capsules)
Hard gelatine capsule, with an opaque white body and opaque yellow cap with “L9NL” and “7.5” printed radial on body. Capsule size: 2
NEOLED 10 mg (hard gelatine capsules)
Hard gelatine capsule, with an opaque yellow body and opaque green cap with “L9NL” and “10” printed radial on body. Capsule size: 0
NEOLED 15 mg (hard gelatine capsules)
Hard gelatine capsule, with an opaque white body and opaque blue cap with “L9NL” and “15” printed radial on body. Capsule size: 0
NEOLED 20 mg (hard gelatine capsules)
Hard gelatine capsule, with an opaque blue body and opaque green cap with “L9NL” and “20” printed radial on body. Capsule size: 0

NEOLED 25 mg (hard gelatine capsules)
Hard gelatine capsule, with an opaque white body and opaque white cap with “L9NL” and “25” printed radial on body. Capsule size: 0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelodysplastic Syndromes (MDS):

NEOLED 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:

NEOLED in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.

4.2 Posology and method of administration

Posology

Myelodysplastic syndromes (MDS):

The recommended starting dose of NEOLED 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 Return to ≥ 50 x 10^9/l	Interrupt NEOLED treatment Resume NEOLED 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 NEOLED treatment
If baseline ≥ 60 x 10^9/l and returns to ≥ 50 x 10^9/l	Resume NEOLED 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 NEOLED 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 NEOLED treatment
Return to ≥ 30 x 10^9/l (without signs of bleeding)	Resume NEOLED at 5 mg once a day continuously in repeating 28 days cycles

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

If thrombocytopenia develops during treatment at 5 mg daily

When Platelets	Recommended Course
< 30 x 10^9/l or < 50 x 10^9/l with platelet transfusions	Interrupt NEOLED treatment
Return to ≥ 30 x 10^9/l (without signs of bleeding)	Resume NEOLED at 5 mg every other day

Neutrophil counts (ANC)+
Patients who are dosed initially at 10 mg and experience neutropenia should have their dosage adjusted as follows:

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

If baseline ANC ≥ 1 x 10^9/l	
When Neutrophils	Recommended Course
Fall to < 0,75 x 10^9/l	Interrupt NEOLED treatment
Return to ≥ 1 x 10^9/l	Resume NEOLED at 5 mg once a day continuously in repeating 28 day cycles
If baseline ANC < 1 x 10^9/l	
When Neutrophils	Recommended Course
Fall to < 0,5 x 10^9/l	Interrupt NEOLED treatment
Return to ≥ 0,5 x 10^9/l	Resume NEOLED 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 NEOLED treatment
Return to ≥ 0,5 x 10^9/l	Resume NEOLED at 5 mg once a day continuously in repeating 28 day cycles
+ Absolute neutrophil count	

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

If neutropenia develops during treatment at 5 mg daily

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

Discontinuation of NEOLED
NEOLED interruption or discontinuation should be considered for Grade 2-3 skin rash. NEOLED 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 NEOLED 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 NEOLED.

Platelet counts
Thrombocytopenia
See table below entitled, 'Dose Reduction Steps for NEOLED in Previously Treated Multiple Myeloma'.

Neutrophil counts (ANC)
Neutropenia
See table below entitled, 'Dose Reduction Steps for NEOLED in Previously Treated Multiple Myeloma'.

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

Discontinuation of NEOLED
NEOLED interruption or discontinuation should be considered for Grade 2-3 skin rash. NEOLED 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 NEOLED 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 NEOLED treatment and follow CBC weekly	Starting dose	25 mg
Return to ≥ 30 x 10^9/l	Resume NEOLED 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 NEOLED treatment Resume NEOLED at the next lower dose level -2 or -3 for the indicated dose regimen. Do not dose below the lowest NEOLED 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 [a]	Dose Level	Previously Treated Multiple Myeloma (combination with dexamethasone) Days 1-21/28 day cycle

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

[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 NEOLED.

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

Discontinuation of NEOLED
NEOLED interruption or discontinuation should be considered for Grade 2-3 skin rash. NEOLED 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 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 NEOLED 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:
NEOLED 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 (CL_{cr}) ≥ 60 mL/min. The following NEOLED dose adjustments are recommended at the start of therapy for patients with CL_{cr} < 60 mL/min.

Renal Function (CL_{cr})	**Starting dose 25 mg**	**Starting dose 10 mg**
Moderate Renal Impairment (30 > CL_{cr} < 60mL/min)	10 mg [a] Every 24 hours	5 mg Every 24 hours
Severe Renal Impairment (CL_{cr} < 30 mL/min, not requiring dialysis)	15 mg Every 48 hours	5 mg Every 48 hours
End Stage Renal Disease (CL_{cr} < 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

CL_{cr} = 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 NEOLED therapy, subsequent NEOLED 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. NEOLED is not known to be metabolised by the liver; the elimination of unchanged NEOLED is predominantly by the renal route (see Section 5.2).

Method of administration

NEOLED should be taken orally at about the same time each day. The capsules should not be opened, broken, or chewed. NEOLED 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 to any of the excipients listed in section 6.1.
- Pregnancy and lactation (see sections 4.4 and 4.6).
- 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

When NEOLED is given in combination with other medicines, the corresponding Professional Information must be consulted prior to initiation of treatment.

Pregnancy warning
NEOLED is contraindicated during pregnancy.

SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS.
NEOLED 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 NEOLED 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 NEOLED AS NEGLIGIBLE AS POSSIBLE, NEOLED IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME. THIS PROGRAMME IS CALLED THE KEY ASSIST RISK MANAGEMENT PROGRAM.
UNDER THIS RESTRICTED DISTRIBUTION PROGRAMME, ONLY PRECRIBERS 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 KEY ASSIST RISK MANAGEMENT PROGRAM.

The conditions of the Key Assist 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, NEOLED 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, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
- Even if a woman of childbearing potential has amenorrhoea, she must follow all the advice on effective contraception
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy
- She understands the need to commence the treatment as soon as lenalidomide is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing at least 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 NEOLED.

For male patients taking NEOLED, 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 stopping the substance in the healthy subject (see section 5.2). As a precaution and taking into account special populations with prolonged elimination time such as renal impairment, all male patients taking
NEOLED must meet the following conditions:

- Understand the expected teratogenic risk if engaged in sexual activity with a pregnant woman or a woman of childbearing potential.
- Understand the need for the use of a condom if engaged in sexual activity with a pregnant woman or a woman of childbearing potential not using effective contraception (even if the man has had a vasectomy), during treatment and for 4 weeks after dose interruptions and/or cessation of treatment.
- Understand that if his female partner becomes pregnant whilst he is taking NEOLED or shortly after he has stopped taking NEOLED, he should inform his treating medical practitioner immediately and that it is recommended to refer the female partner to a medical practitioner specialised or experienced in teratology for evaluation and advice.
- Male patients taking NEOLED should not donate sperm or semen during treatment, including dose interruptions and for 4 weeks following cessation of treatment.

The prescriber must ensure that for women of childbearing potential:

- The patient complies with the conditions of the Pregnancy Prevention Programme, including confirmation that she has an adequate level of understanding
- The patient has acknowledged the aforementioned conditions.

Contraception

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

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

- Implant
- Levonorgestrel-releasing intrauterine system (IUS)
- Medroxyprogesterone acetate depot
- Tubal sterilisation
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses
- Ovulation inhibitory progesterone-only pills (i.e. desogestrel)

Effective methods

- Male condoms
- Diaphragm
- Cervical cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking NEOLED in combination therapy, and to a lesser extent in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma taking NEOLED 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. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone (see section 4.5).

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

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

Pregnancy testing

According to local practice, medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for women of childbearing potential as outlined below. This requirement includes women of childbearing potential who practice absolute and continuous abstinence. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of NEOLED to women of childbearing potential should occur within 7 days of the prescription.

Prior to starting treatment

A medically supervised pregnancy test should be performed during the consultation, when NEOLED is prescribed, or in the 7 days prior to the visit to the prescriber once the patient had been using effective contraception for at least 4 weeks.
The test should ensure the patient is not pregnant when she starts treatment with NEOLED.

Follow-up and end of treatment

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

Additional precautions

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

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

Educational materials, prescribing and dispensing restrictions

In order to assist patients in avoiding foetal exposure to NEOLED, the marketing authorisation holder will provide educational material to health care professionals to reinforce the warnings about the expected teratogenicity of lenalidomide, to provide advice on contraception before therapy is started, and to provide guidance on the need for pregnancy testing. The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the Pregnancy Prevention Programme and provide patients with appropriate patient educational brochure, patient card and/or equivalent tool in accordance to the national implemented patient card system. A national controlled distribution system has been implemented in collaboration with each National Competent Authority. The controlled distribution system includes the use of a patient card and/or equivalent tool for prescribing and/or dispensing controls, and the collecting of detailed data relating to the indication in order to monitor closely the off-label use within the national territory. Ideally, pregnancy testing, issuing a prescription and dispensing should occur on the same day. Dispensing of NEOLED 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 NEOLED, particularly in those with known risk factors and within the first 12 months when used in combination with dexamethasone. Patients with known risk factors – including prior thrombosis – should be closely monitored, and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Venous and arterial thromboembolic events

In patients with multiple myeloma, the combination of NEOLED with dexamethasone is associated with an increased risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism).

In patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma, treatment with NEOLED monotherapy was associated with a lower risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism) than in patients with multiple myeloma treated with NEOLED in combination therapy (see sections 4.5 and 4.8).

In patients with multiple myeloma, the combination of NEOLED with dexamethasone is associated with an increased risk of arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event). The risk of arterial thromboembolism is lower in patients with multiple myeloma treated with NEOLED monotherapy than in patients with multiple myeloma treated with NEOLED in combination therapy.

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic medicines or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic medicines, or other medicines that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving NEOLED with dexamethasone. A haemoglobin concentration above 12 g/dl should lead to discontinuation of erythropoietic medicines.

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

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

In case of neutropenia, the medical practitioner 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 (see section 4.8, Haemorrhagic disorders).

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

Myelodysplastic syndromes (MDS)
Haematologic toxicity (neutropenia and thrombocytopenia) in deletion 5q MDS – A complete blood cell count, including white blood cell count with differential, platelet count, haemoglobin, and haematocrit should be performed weekly for first 8 weeks of NEOLED treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2).

NEOLED treatment in myelodysplastic syndromes patients is associated with a higher incidence of grade 3 and 4 neutropenia and thrombocytopenia compared to patients on placebo (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.

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

Tumour flare reaction and tumour lysis syndrome
Because NEOLED has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have frequently been observed in patients with chronic lymphocytic leukemia (CLL), and less frequently in patients with lymphomas, who were treated with lenalidomide e.g. NEOLED. Fatal instances of TLS have been reported during treatment with lenalidomide as in NEOLED. The patients at risk of TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to NEOLED. 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 NEOLED, and no reports in patients with MDS treated with NEOLED.

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

Severe skin reactions
Severe cutaneous reactions including SJS, and TEN and DRESS have been reported with the use of NEOLED. 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. NEOLED must be discontinued for exfoliative or bullous rash, or if SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions. Interruption or discontinuation of NEOLED should be considered for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with thalidomide treatment should not receive NEOLED.

Second primary malignancies
- Previously treated MM

A numerical imbalance was observed in clinical trials in previously treated multiple myeloma patients with NEOLED/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.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS
- *Karyotype*

Baseline variables including complex cytogenetics are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality. Reports have shown in a combined analysis of two clinical trials of lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes, subjects who had a complex cytogenetics had the highest estimated 2-year cumulative risk of progression to AML (38,6 %). The estimated 2-year rate of progression to AML in patients with an isolated Del (5q) abnormality was 13,8 %, compared to 17,3 % for patients with Del (5q) and one additional cytogenetic abnormality.
As a consequence, the benefit/risk ratio of NEOLED when MDS is associated with Del (5q) and complex cytogenetics is unknown.

- *TP53 status*

A TP53 mutation is present in 20 to 25 % of lower-risk MDS Del 5q patients and is associated with a higher risk of progression to acute myeloid leukaemia (AML). In a post-hoc analysis of a clinical trial of lenalidomide in low- or intermediate-1-risk myelodysplastic syndromes (MDS-004), the estimated 2-year rate of progression to AML was 27,5 % in patients with IHC-p53 positivity (1 % cut-off level of strong nuclear staining, using immunohistochemical assessment of p53 protein as a surrogate for TP53 mutation status) and 3,6 % in patients with IHC-p53 negativity (p=0,0038) (see section 4.8)

Hepatic disorders
Hepatic failure, including fatal cases, has been reported in patients treated with NEOLED 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.

NEOLED 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 NEOLED is combined with medicines known to be associated with liver dysfunction.

Infection with or without neutropenia
Patients with multiple myeloma are prone to develop infections including pneumonia. Patients with known risk factors for infections should be closely monitored. All patients should be advised to seek medical attention promptly at the first sign of infection (e.g. cough, fever, etc) thereby allowing for early management to reduce severity.

Viral reactivation
Cases of viral reactivation have been reported in patients receiving 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 NEOLED 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 NEOLED and adequate antiviral treatment. Hepatitis B virus status should be established before initiating treatment with NEOLED. 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 NEOLED 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 NEOLED. PML was reported several months to several years after starting the treatment with NEOLED. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. Medical practitioners should monitor patients at regular intervals and should consider PML in the differential diagnosis in patients with new or worsening neurological symptoms, cognitive or behavioural signs or symptoms. Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

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

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

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

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

4.5 Interaction with other medicines and other forms of interaction
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 NEOLED with dexamethasone (see sections 4.4 and 4.8).

Oral contraceptives
No interaction study has been performed with oral contraceptives. Lenalidomide as in NEOLED is not an enzyme inducer. In an *in vitro* study with human hepatocytes, lenalidomide, at various concentrations tested did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicines, including hormonal contraceptives, is not expected if NEOLED 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).
Patients with multiple myeloma or MDS monotherapy taking combined oral contraceptive pills or hormone replacement therapy, have an increased risk of venous thromboembolic events (VTE).

Warfarin
Co-administration of multiple 10 mg doses of NEOLED had 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 lenalidomide. 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
When digoxin was co-administered with NEOLED (10 mg/day) the digoxin C_{max} and AUC0-∞ were 14 % higher than when digoxin was administered concomitantly with placebo. Periodic monitoring of digoxin plasma levels is recommended during administration of NEOLED.

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

Dexamethasone
Co-administration of single or multiple doses of dexamethasone (40 mg once daily) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg once daily).

Interactions with P-glycoprotein (P-gp) inhibitors
In vitro, lenalidomide is a 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 lenalidomide (25 mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

4.6 Fertility, pregnancy and lactation
Women of childbearing potential / Contraception in females
Women of childbearing potential should use effective method of contraception. If pregnancy occurs in a woman treated with NEOLED, treatment must be stopped immediately, and the patient should be referred to a medical practitioner specialised or experienced in teratology for evaluation and advice. If pregnancy occurs in a partner of a male patient taking NEOLED, it is recommended to refer the female partner to a medical practitioner specialised or experienced in teratology for evaluation and advice.

Clinical data has demonstrated the presence of lenalidomide in human semen. Therefore, male patients taking NEOLED should use a condom during NEOLED therapy including dose interruptions and for 4 weeks after cessation of treatment. Male patients taking NEOLED 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 (Amenorrhoea following cancer therapy or during breastfeeding 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.

Pregnancy
NEOLED is contraindicated in females who are pregnant or who could become pregnant (see section 4.3).
NEOLED 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 therapy, including dose interruptions, and for 28 days following discontinuation of NEOLED therapy, or continually abstain from sexual intercourse.

- There is an increased risk of VTE in patients with multiple myeloma taking NEOLED and dexamethasone, and in patients with MDS taking NEOLED 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 NEOLED.
- If pregnancy does occur, NEOLED should be discontinued immediately.

Breastfeeding
Breastfeeding is contraindicated during therapy with NEOLED (see section 4.3).

Fertility
A fertility study in rats with lenalidomide doses up to 500 mg/kg (approximately 200 to 500 times the human doses of 25 mg and 10 mg, respectively, based on body surface area) produced no adverse effects on fertility and no parental toxicity.

4.7 Effects on ability to drive and use machines
NEOLED may affect the ability to drive and use machines. Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported
with the use of NEOLED. 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/preferred term and frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

b. Tabulated list of adverse reactions

Frequency of ADRs	All ADRs	Grade 3/4 ADRs	SADRs
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	Fatigue, pyrexia, asthenia	

Gastrointestinal Disorders			
Frequent	Diarrhoea[@], vomiting[@], nausea[@], constipation, abdominal pain (including upper)[@], dry mouth, dyspepsia	Diarrhoea[@], nausea[@], constipation, toothache	Diarrhoea[@]
Unknown frequency		Pancreatitis, gastrointestinal perforation (including diverticular, intestinal and large intestine perforations)	
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, musculoskeletal and connective tissue pain and discomfort, back pain	Back pain
Nervous System disorders			
Frequent	Peripheral neuropathies (excluding motor neuropathy), dizziness, tremor, dysgeusia, headache lethargy, paraesthesia	Syncope, dizziness	Cerebrovascular accident[@]
Respiratory, thoracic and mediastinal disorders			
Frequent	Dyspnoea, epistaxis	Respiratory distress[@], bronchitis	
Unknown frequency		Interstitial pneumonitis	

Infections and infestations			
Frequent	Pneumonia[@], bronchitis, bacterial, viral and fungal infections (including opportunistic infections, herpes zoster and hepatitis B virus reactivation), upper respiratory tract infection, sinusitis	Pneumonia[@], bacterial, viral and fungal infections (including opportunistic infections, herpes zoster and hepatitis B virus reactivation)	Pneumonia[@], bacterial, viral and fungal infections (including opportunistic infections)
Skin and subcutaneous tissue disorders			
Frequent	Rash[+], pruritus, dry skin, hyperhidrosis	Rash, pruritus	
Unknown frequency		Angioedema, Stevens-Johnson Syndrome, toxic epidermal necrolysis, leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	
Blood and lymphatic system disorders			
Frequent	Neutropenia[%], thrombocytopenia[@], anaemia[@], leukopenia	Neutropenia[%], thrombocytopenia[@], anaemia[@], leukopenia, febrile neutropenia[%]	Anaemia[@], febrile neutropenia[%], neutropenia[%], thrombocytopenia[@]
Unknown frequency	Acquired haemophilia		
Endocrine disorders			
Frequent	Hypothyroidism		
Metabolism and nutrition disorders			
Frequent	Decreased appetite, iron overload, decreased weight, hypokalaemia,	Hypokalaemia, hypocalcaemia,	Hyperglycaemia[%]

	hypocalcaemia, dehydration, dypomagnesaemia, iron overload	hypophosphataemia, hyperglycaemia[%], decreased appetite	
Eye disorders			
Frequent	Blurred vision	Cataracts	
Renal disorders			
Frequent		Renal failure[@]	Renal failure[@]
Vascular disorders			
Frequent	Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism[@] hypertension, hypotension, haematoma	Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism[@]	Venous thromboembolic events, predominantly deep vein thrombosis and pulmonary embolism[@]
Psychiatric disorders			
Frequent		Depression	Altered mood
Cardiac disorders			
Frequent		Acute myocardial infarction[@], atrial fibrillation[@], tachycardia, cardiac failure congestive[@], cardiac failure[@]	Acute myocardial infarction[@], atrial fibrillation[@], cardiac failure congestive[@], cardiac failure[@]
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Frequent			B-cell lymphomas
Unknown frequency		Tumour lysis syndrome	
Immune system disorders			
Less frequent	Hypersensitivity		
Unknown frequency	Solid organ transplant rejection		

Hepato-biliary Disorders			
Frequent	Abnormal liver function tests	Abnormal liver function tests	Abnormal liver function tests
Unknown frequency	Acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, mixed cytolytic/cholestatic hepatitis	Acute hepatic failure, toxic hepatitis	
Injury, poisoning and procedural complications			
Frequent		Fall	

@ - ADRs with Death as an outcome
% - ADRs which were considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
# - All PTs under SOC of Infections except for rare infections of Public Health interest will be considered listed
+- All PTs under HLT of Rash will be considered listed

c. Description of selected adverse reactions

Teratogenicity

NEOLED 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 sections 4.6 and 5.3). If NEOLED is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

Neutropenia and thrombocytopenia

Multiple myeloma: patients with at least one prior therapy

The combination of NEOLED with dexamethasone in multiple myeloma patients is associated with a higher incidence of grade 4 neutropenia. Grade 4 febrile neutropenia episodes were observed.

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

Myelodysplastic syndromes patients

In myelodysplastic syndromes patients, NEOLED is associated with a higher incidence of grade 3 or 4 neutropenia. Grade 3 or 4 febrile neutropenia episodes were observed. NEOLED is associated with a higher incidence of grade 3 or 4 thrombocytopenia.

Venous thromboembolism

An increased risk of DVT and PE is associated with the use of the combination of NEOLED with dexamethasone in patients with multiple myeloma, or in patients with multiple myeloma, myelodysplastic syndromes treated with NEOLED monotherapy (see section 4.5).

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 NEOLED, particularly in those with known risk factors.

Haemorrhagic disorders
Haemorrhagic disorders are listed under several system organ classes: Blood and lymphatic system disorders; nervous system disorders (intracranial haemorrhage); respiratory, thoracic and mediastinal disorders (epistaxis); gastrointestinal disorders (gingival bleeding, haemorrhoidal haemorrhage, rectal haemorrhage); renal and urinary disorders (haematuria); injury, poisoning and procedural complications (contusion) and vascular disorders (ecchymosis).

Allergic reactions
Cases of allergic reaction/hypersensitivity reactions have been reported. A possible cross-reaction between lenalidomide (e.g. NEOLED) and thalidomide has been reported in the literature.

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

Second primary malignancies
In clinical trials in previously treated myeloma patients with lenalidomide/dexamethasone compared to controls, mainly comprising of basal cell or squamous cell skin cancers.

Acute myeloid leukaemia
Myelodysplastic syndromes
Baseline variables including complex cytogenetics and TP53 mutation are associated with progression to AML in subjects who are transfusion dependent and have a Del (5q) abnormality (see section 4.4).

Hepatic disorders
The following post-marketing 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 NEOLED is administered with a statin.

Thyroid disorders
Cases of hypothyroidism and cases of hyperthyroidism have been reported (see section 4.4 Thyroid disorders).

Tumour flare reaction and tumour lysis syndrome
It has been reported in study MCL-002, approximately 10 % of lenalidomide-treated patients experienced TFR compared to 0 % in the control arm. The majority of the events occurred in cycle 1, all were assessed as treatment-related, and the majority of the reports were Grade 1 or 2. Patients with high MIPI at diagnosis or bulky disease (at least one lesion that is ≥ 7 cm in the longest diameter) at baseline may be at risk of TFR. In study MCL-002, TLS was reported for one patient in each of the two treatment arms. In the supportive study MCL-001, approximately 10 % of subjects experienced TFR; all report

were Grade 1 or 2 in severity and all were assessed as treatment-related. The majority of the events occurred in cycle 1. There were no reports of TLS in study MCL-001 (see section 4.4).

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

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 professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose
There is no specific experience in the management of NEOLED 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
Pharmaceutical classification: A32 Other- Immunomodulators
Pharmacotherapeutic group: Other immunosuppressants. ATC code: L04AX04.

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

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

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

5.2 Pharmacokinetic properties

Absorption

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

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

In multiple myeloma patients (baseline serum creatinine level ≤ 1,5 mg/dl), C_{max} occurs between 0,5 to 6 hours post dose. Plasma exposure (AUC and C_{max}) increases proportionally with dose following single and multiple doses. Multiple doses at 25 mg/day do not cause lenalidomide to accumulate in plasma. Exposure (AUC) in multiple myeloma patients is higher compared to healthy volunteers since lenalidomide clearance is lower in these patients than in healthy volunteers. This is consistent with the compromised renal function in the multiple myeloma patients (dose adjustments are recommended for patients with CLcr < 60 mL/min; see ‘section 4.2’ 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 ‘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 volunteers and 23 % in multiple myeloma patients.

Lenalidomide is present in semen (< 0,01 % of the dose) after administration of 25 mg/day and the substance is undetectable in semen 3 days after stopping the lenalidomide (see section 4.4).

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

Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy volunteers, approximately 90 % and 4 % of the radioactive dose is eliminated in urine and faeces, respectively. Approximately 82 % of the radioactive dose is excreted as lenalidomide, almost exclusively via the urinary route. 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 volunteers and ranged from 3 to 5 hours in patients with multiple myeloma or MDS.

Characteristics in specific groups of subjects or patients
Children:
No data are available.

Older people
No data are available

Renal impairment
The pharmacokinetics of lenalidomide was studied in subjects with renal impairment due to non-malignant conditions.
In this study, 5 patients with mild renal function impairment (creatinine clearance (CLcr) 56-74 ml/min), 6 patients with moderate renal function impairment (CLcr 33-46 ml/min), 6 patients with severe renal function impairment (CLcr 17-29 ml/min), and 6 patients with end stage renal disease requiring dialysis were administered a single 25 mg oral dose of lenalidomide. A single oral 25 mg dose of lenalidomide were administered to 7 healthy subjects of similar age with normal renal function (CLcr 83-145 ml/min). The pharmacokinetics of lenalidomide were similar in patients with mild impairment CLcr 56-74 ml/min and healthy subjects. Moderately and severely impaired patients had a 3-fold increase in half-life and a 66 % to 75 % decrease in clearance compared to that of healthy subjects. Patients on haemodialysis had an approximate 4,5-fold increase in half-life and an 80 % decrease in clearance compared to healthy subjects. Approximately 30 % of the substance in the body was removed by a 4-hour dialysis session.

Hepatic impairment
No data are available

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Cellulose, microcrystalline
Croscarmellose sodium
Lactose
Magnesium stearate

Capsule shell
<u>NEOLED 2,5 & 10 & 20 mg</u>
Gelatine
Indigotine – FD&C Blue #2 (E132)
Titanium dioxide (E171)
Yellow iron oxide (E172)
<u>NEOLED 5 & 25 mg</u>
Gelatine
Titanium dioxide (E171)

NEOLED 7,5 mg
Gelatine
Titanium dioxide (E171)
Yellow iron oxide (E172)
NEOLED 15 mg
Gelatine
Titanium dioxide (E171)
Indigotine – FD&C Blue #2 (E132)

Capsule ink
Iron oxide black (E172)
Potassium hydroxide (E525)
Propylene glycol (E1520)
Shellac (E904)
Strong ammonia solution (E527)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at or below 25 °C.
Keep the capsule in the blister in the outer carton until required for use.

6.5 Nature and contents of container
The capsules are packed in an oPA/Al/PVC/Al blisters (packed in carton boxes).
Pack sizes: 7, 21 or 28 capsules.
Not all strengths and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Capsules should not be opened or crushed. If powder from lenalidomide makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If lenalidomide makes contact with the mucous membranes, they should be thoroughly flushed with water.
Any unused medicine or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road
Midrand
1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)
NEOLED 2,5 mg 54/32/0540
NEOLED 5 mg 54/32/0541
NEOLED 7,5 mg 54/32/0542
NEOLED 10 mg 54/32/0543
NEOLED 15 mg 54/32/0544
NEOLED 20 mg 54/32/0545
NEOLED 25 mg 54/32/0546

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24 July 2020

10. DATE OF REVISION OF THE TEXT

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