PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1 NAME OF THE MEDICINE

LENALIDOMIDE DRL 5, 5 mg, hard gelatin capsules

LENALIDOMIDE DRL 10, 10 mg, hard gelatin capsules

LENALIDOMIDE DRL 15, 15 mg, hard gelatin capsules

LENALIDOMIDE DRL 25, 25 mg, hard gelatin capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LENALIDOMIDE DRL 5

Each hard gelatin capsule contains lenalidomide 5 mg.

Excipient(s) with known effect: Contains sugar.

Contains approximately 14 mg sugar (mannitol) per capsule.

LENALIDOMIDE DRL 10

Each hard gelatin capsule contains lenalidomide 10 mg.

Excipient(s) with known effect: Contains sugar.

Contains approximately 28 mg sugar (mannitol) per capsule.

LENALIDOMIDE DRL 15

Each hard gelatin capsule contains lenalidomide 15 mg.

Excipient(s) with known effect: Contains sugar.

Contains approximately 42 mg sugar (mannitol) per capsule.

LENALIDOMIDE DRL 25

Each hard gelatin capsule contains lenalidomide 25 mg.

Excipient(s) with known effect: Contains sugar.

Contains approximately 70 mg sugar (mannitol) per capsule.

For the full list of excipients, see section 6.1.

WARNING: SEVERE LIFE-THREATENING HUMAN BIRTH DEFECTS.

Lenalidomide is structurally related to thalidomide, a known human teratogenic active substance that causes severe life-threatening birth defects. Lenalidomide induced 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 DRL AS NEGLIGIBLE AS POSSIBLE, LENALIDOMIDE DRL IS APPROVED FOR MARKETING UNDER A SPECIAL RESTRICTED DISTRIBUTION PROGRAMME. THIS PROGRAMME IS CALLED LEN PERM (PROGRAM FOR THE EVALUATION OF RISK AND MANAGEMENT).

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 LEN PERM (PROGRAM FOR THE EVALUATION OF RISK AND MANAGEMENT).

3 PHARMACEUTICAL FORM

Hard gelatin capsules.

LENALIDOMIDE DRL 5

White to off-white coloured powder filled in size ‘4’ hard gelatin capsules with opaque white coloured cap imprinted ‘RDY’ with black ink and opaque white colored body imprinted ‘5 mg’ with black ink.

LENALIDOMIDE DRL 10

White to off-white coloured powder filled in size ‘2’ hard gelatin capsules with pale green coloured cap imprinted ‘RDY’ with black ink and pale yellow coloured body imprinted ’10 mg’ with black ink.

LENALIDOMIDE DRL 15

White to off-white coloured powder filled in size ‘1’ hard gelatin capsules with blue coloured cap imprinted ‘RDY’ with black ink and white coloured body imprinted ’15 mg’ with black ink.

LENALIDOMIDE DRL 25

White to off-white coloured powder filled in size ‘0’ hard gelatin capsules with opaque white coloured cap imprinted ‘RDY’ with black ink and opaque white coloured body imprinted ’25 mg’ with black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Myelodysplastic Syndromes (MDS)

LENALIDOMIDE DRL 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

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

4.2 Posology and method of administration

Posology

Myelodysplastic syndromes (MDS)

Recommended dosage

The recommended starting dose of LENALIDOMIDE DRL 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:

<u>If thrombocytopenia develops WITHIN 4 weeks of starting treatment at 10 mg:</u>

If baseline ≥ 100 x 10^9/L	
When platelets	Recommended course
Fall to < 50 x 10^9/L	Interrupt LENALIDOMIDE DRL treatment
Return to ≥ 50 x 10^9/L	Resume LENALIDOMIDE DRL 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 DRL treatment
If baseline ≥ 60 x 10^9/L and returns to ≥ 50 x 10^9/L	Resume LENALIDOMIDE DRL 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 DRL 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 LENALIDOMIDE DRL treatment
Return to ≥ 30 x 10^9/L (without signs of bleeding)	Resume LENALIDOMIDE DRL at 5 mg once a day continuously in repeating 28 day cycles

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

If thrombocytopenia develops during treatment at 5 mg daily:

When platelets	Recommended course
< 30 x 10^9/L or < 50 x 10^9/L with platelet transfusions	Interrupt LENALIDOMIDE DRL treatment
Return to ≥ 30 x 10^9/L (without signs of bleeding)	Resume LENALIDOMIDE DRL 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 LENALIDOMIDE DRL treatment
Return to ≥ 1 x 10^9/L	Resume LENALIDOMIDE DRL 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 LENALIDOMIDE DRL treatment
Return to ≥ 0,5 x 10^9/L	Resume LENALIDOMIDE DRL at 5 mg once a day continuously in repeating 28 day cycles

<u>If neutropenia develops AFTER 4 weeks of starting treatment at 10 mg:</u>

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 ºC)	Interrupt LENALIDOMIDE DRL treatment
Return to ≥ 0,5 x 10^9/L	Resume LENALIDOMIDE DRL 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:

<u>If neutropenia develops during treatment at 5 mg daily:</u>

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 ºC)	Interrupt LENALIDOMIDE DRL treatment
Return to ≥ 0,5 x 10^9/L	Resume LENALIDOMIDE DRL 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 DRL, 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 DRL

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

LENALIDOMIDE DRL 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 LENALIDOMIDE DRL 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 DRL.

Platelet counts

Thrombocytopenia

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

Neutrophil counts (ANC)

Neutropenia

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

Other Grade 3/4 Toxicities

For other Grade 3/4 toxicities judged to be related to LENALIDOMIDE DRL, 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 DRL

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

Platelet counts

Thrombocytopenia

When platelets	Recommen-ded Course	Dose Levels	Previously Treated Multiple

			Myeloma (combination with dexametha-sone)
			Days 1-21/28 day cycle
Fall to < 30 x 10^9/L	Interrupt LENALIDO-MIDE DRL treatment and follow CBC weekly	Starting Dose	25 mg
Return to ≥ 30 x 10^9/L	Resume LENALIDO-MIDE DRL at dose level -1	Dose Level -1	15 mg
For each subsequent drop below < 30 x 10^9/L	Interrupt LENALIDO-MIDE DRL treatment	Dose Level -2	10 mg
Return to ≥ 30 x 10^9/L	Resume LENALIDO-MIDE DRL at the next lower dose level -2	Dose Level -3	5 mg

	or -3 for the indicated dose regimen. Do not dose below the lowest LENALIDO-MIDE DRL dose level in the indicated dose regimen.		

Absolute neutrophil counts (ANC)

Neutropenia

When neutrophils	Recommen-ded Course[a]	Dose Level	Previously Treated Multiple Myeloma (combination with dexametha-sone)
			Days 1-21/28 day cycle
Fall to < 0,5 x 10^9/L	Interrupt LENALIDO-	Starting Dose	25 mg

	MIDE DRL treatment and follow CBC weekly		
Return to ≥ 0,5 x 10^9/L	Resume LENALIDO-MIDE DRL 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 LENALIDO-MIDE DRL treatment Resume LENALIDO-MIDE DRL at the next lower dose level -2 or -3 for the indicated dose regimen. Do not dose below the lowest LENALIDO-MIDE DRL dose level in	Dose Level -2	10 mg
		Dose Level -3	5 mg

	the indicated dose regimen.		

a At the medical practitioner's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of LENALIDOMIDE DRL.

Other Grade 3/4 Toxicities

For other Grade 3/4 toxicities judged to be related to LENALIDOMIDE DRL, 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 DRL

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

- *Paediatric population:*

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

Method of administration

Oral use.

LENALIDOMIDE DRL should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken, or chewed. LENALIDOMIDE DRL 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.
- Women of childbearing potential, except when all of the conditions for pregnancy prevention have been met (see sections 4.4 and 4.6).

4.4 Special warnings and precautions for use

General

When LENALIDOMIDE DRL is given in combination with other medicines, the corresponding professional information must be consulted prior to initiation of treatment.

A 3-month prescription (12 weeks supply) is allowed for males and females **with a permanent** non-childbearing potential.

Pregnancy warning

LENALIDOMIDE DRL is contra-indicated during pregnancy.

Lenalidomide 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 DRL is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected.

The conditions of LEN PERM (PROGRAM FOR THE EVALUATION OF RISK AND MANAGEMENT) 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 DRL is contraindicated unless all of the following are met:

- She understands the expected teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting treatment, throughout the entire duration of treatment including dose interruptions, and for 6 months after the end of treatment
- Even if a woman of childbearing potential has 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 DRL 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 DRL.

For male patients taking LENALIDOMIDE DRL, pharmacokinetic data has demonstrated that lenalidomide is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after discontinuation of lenalidomide in the healthy subject (see section 5.2). As a precaution all male patients taking LENALIDOMIDE DRL 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 LEN PERM (PROGRAM FOR THE EVALUATION OF RISK AND MANAGEMENT), 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 6 months after LENALIDOMIDE DRL 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 DRL and dexamethasone, and in patients with myelodysplastic syndromes taking LENALIDOMIDE DRL 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 DRL 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 DRL 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 DRL.

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

Additional precautions

Patients should not donate blood during therapy including dose interruptions and for 3 months following discontinuation of LENALIDOMIDE DRL.

Educational materials

In order to assist patients in avoiding foetal exposure to LENALIDOMIDE DRL, educational material will be provided to health care professionals to reinforce the warnings about the expected teratogenicity of LENALIDOMIDE DRL, 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 Len Perm Programme for the evaluation of risk management 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

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

Venous and arterial thromboembolic events

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

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

Pulmonary hypertension

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

Neutropenia and thrombocytopenia

The major dose limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A dose reduction may be required (see section 4.2).

In case of neutropenia, the medical practitioner should monitor for signs of infection. 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 epistaxes, especially in patients receiving concomitant medicines susceptible to induce bleeding.

Co-administration of LENALIDOMIDE DRL with other myelosuppressive agents should be undertaken with caution.

- Multiple myeloma: patients with at least one prior therapy

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

- 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 LENALIDOMIDE DRL treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2).

Second primary malignancies

- Previously treated MM

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

Carefully evaluate patients before and during treatment using standard cancer screening

for occurrence of second primary malignancies and institute treatment as appropriate.

Thyroid disorders

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

Peripheral neuropathy

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

Tumour flare reaction and tumour lysis syndrome

Because lenalidomide has anti-neoplastic activity the complications of tumour lysis syndrome (TLS) may occur. TLS and tumour flare reaction (TFR) have commonly been observed in patients with chronic lymphocytic leukemia (CLL), and in patients with lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. 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 LENALIDOMIDE DRL. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been rare reports of TLS in patients with MM treated with lenalidomide.

Allergic conditions / Severe skin reactions

Angioedema and severe cutaneous reactions including SJS, and TEN and DRESS have been reported. These events can be fatal. Patients should be advised of the signs and symptoms of these reactions by their medical practitioners and should be told to seek medical attention immediately if they develop these symptoms.

Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive LENALIDOMIDE DRL. LENALIDOMIDE DRL interruption or discontinuation should be considered for Grade 2-3 skin rash. LENALIDOMIDE DRL must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if

SJS, TEN or DRESS is suspected, and should not be resumed following discontinuation for these reactions.

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.

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.

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 (eg, cough, fever, etc) thereby allowing for early management to reduce severity.

Viral reactivation

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

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

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

Reactivation of hepatitis B has been reported rarely in patients receiving lenalidomide who have previously been infected with the hepatitis B virus (HBV). Some of these cases have progressed to acute hepatic failure resulting in discontinuation of lenalidomide and adequate antiviral treatment. Hepatitis B virus status should be established before initiating

treatment with lenalidomide. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. Caution should be exercised when LENALIDOMIDE DRL is used in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.

Progressive multifocal leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML), including fatal cases, have been reported with lenalidomide. PML was reported several months to several years after starting the treatment with lenalidomide. Cases have generally been reported in patients taking concomitant dexamethasone or prior treatment with other immunosuppressive chemotherapy. 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.

Cataract

Cataract has been reported with a higher frequency in patients receiving lenalidomide in combination with dexamethasone. Regular monitoring of visual ability is recommended.

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 DRL is not likely to result in clinically relevant medicine interactions.

In vitro studies demonstrate that lenalidomide 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 agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in multiple myeloma patients receiving LENALIDOMIDE DRL with dexamethasone (see sections 4.4 and 4.8).

Patients with multiple myeloma taking LENALIDOMIDE DRL and dexamethasone, patients with MDS taking LENALIDOMIDE DRL monotherapy, as well as patients taking combined oral contraceptive pills or hormone replacement therapy, have an increased risk of venous thromboembolic events (VTE).

Oral contraceptives

No interaction study has been performed with oral contraceptives. Lenalidomide 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 LENALIDOMIDE DRL is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see sections 4.4 and 4.6).

Warfarin

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics and pharmacodynamics of R- and S-warfarin. Coadministration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. 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 lenalidomide (10 mg/day) the digoxin C_{max} and $AUC_{0-\infty}$ were 14 % higher than when digoxin was administered concomitantly with placebo.

Periodic, monitoring of the digoxin concentration is advised during LENALIDOMIDE DRL treatment.

Statins

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

Dexamethasone

In patients with multiple myeloma, co-administration of single or multiple doses of dexamethasone (40 mg once daily) had no significant effect on the multiple dose pharmacokinetics of lenalidomide (25 mg once daily).

Interactions with P-glycoprotein (P-gp) inhibitors

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

4.6 Fertility, pregnancy and lactation

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

Pregnancy

LENALIDOMIDE DRL 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 DRL therapy including dose interruptions, and for 6 months following discontinuation of LENALIDOMIDE DRL therapy, or continually abstain from sexual intercourse. There is an increased risk of VTE in patients with multiple myeloma taking LENALIDOMIDE DRL and dexamethasone, and in patients with MDS taking LENALIDOMIDE DRL

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 DRL.
- If pregnancy does occur during treatment, LENALIDOMIDE DRL should be immediately discontinued.
- Female sexual partners (of childbearing potential) of male patients receiving LENALIDOMIDE DRL, should be advised to use highly effective contraception, during treatment and for 6 months after the last dose of LENALIDOMIDE DRL.

Males:

- Clinical data has demonstrated the presence of lenalidomide in human semen. Therefore, male patients taking LENALIDOMIDE DRL should use a condom during LENALIDOMIDE DRL therapy including dose interruptions and for 3 months after cessation of treatment. Male patients taking LENALIDOMIDE DRL should not donate sperm or semen during treatment including dose interruptions and for 3 months following the discontinuation of treatment.
- Men should be advised not to father a child while receiving treatment and must use highly effective contraception during treatment and for at least 3 months after 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.

Lactation

Breastfeeding is contra-indicated during therapy with LENALIDOMIDE DRL.

4.7 Effects on ability to drive and use machines

LENALIDOMIDE DRL **may affect** the ability to drive and use machines.

Fatigue, dizziness, somnolence, vertigo and blurred vision have been reported with the use of LENALIDOMIDE DRL. Therefore, caution is recommended when driving or using machines.

4.8 Undesirable effects

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.

System Organ Class/ Preferred Term	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, fall	
Gastrointestinal Disorders	Frequent	Diarrhoea[@], vomiting[@], nausea[@],	Diarrhoea[@], nausea[@], constipation,	Diarrhoea[@]

		constipation, abdominal pain (including upper)[@], dry mouth, dyspepsia	toothache	
Musculo-skeletal and Connective Tissue Disorders	Frequent	Musculo-skeletal 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, dysguesia, headache, lethargy, paraesthesia	Syncope, dizziness	Cerebrovascular accident[@]
Respiratory, Thoracic and Mediastinal Disorders	Frequent	Dyspnoea, epistaxis	Respiratory distress[@], bronchitis	
	Less frequent	Pulmonary hypertension	Pulmonary hypertension	
Infections and Infestations#	Frequent	Pneumonia[@], bronchitis, bacterial, viral and fungal infections (including opportunistic infections), upper respiratory tract infection, sinusitis	Pneumonia[@], bacterial, viral and fungal infections (including opportunistic infections)	Pneumonia[@], bacterial, viral and fungal infections (including opportunistic infections)
Skin and	Frequent	Rash+,	Rash, pruritus	

Subcutaneous Tissue Disorders		pruritus, dry skin, hyperhidrosis		
Blood and Lymphatic System Disorders	Frequent	Neutropenia[%], thrombo-cytopenia[@], anaemia[@], leukopenia	Neutropenia[%], thrombocyte-penia[@] anaemia[@], leukopenia, febrile neutropenia[%]	Anaemia[@], febrile neutropenia[%], neutropenia[%], thrombocyte-penia[@]
Metabolism and Nutrition Disorders	Frequent	Decreased appetite, hypokalaemia, hypocalcaemia, dehydration, hypomagne-saemia, iron overload	Hypokalaemia, hypocalcaemia, hypophosphata emia, hyperglycaemia [%], decreased appetite	Hyperglycaemia [%]
Eye Disorders	Frequent	Blurred vision	Cataracts	
Renal and Urinary 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,	Frequent			B-cell lymphomas

Malignant and Unspecified (including cysts and polyps				
Immune System Disorders	Less frequent	Hypersensi-tivity		
Hepatobiliary Disorders	Frequent	Abnormal liver function tests	Abnormal liver function tests	Abnormal liver function tests
Investigations	Frequent	Decreased weight		

@ - ADRs with Death as an outcome
% - ADRs which were considered to be Life Threatening (if the outcome of the event was death, it is included with death cases)
# - All 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

The following adverse drug reactions have been identified from the worldwide postmarketing experience with lenalidomide. Allergic conditions (angioedema, SJS, TEN), tumour lysis syndrome (TLS) and tumour flare reaction (TFR), pneumonitis, and transient abnormal liver laboratory tests have been reported, but the frequency is unknown.

Hepatic Disorders

Transient liver laboratory abnormalities (predominantly transaminases) were reported in patients treated with lenalidomide. Treatment with LENALIDOMIDE DRL should be interrupted and restarted once the levels return to baseline. Successful re-challenge without recurrence of liver laboratory elevation was reported in some patients.

Reporting of suspected adverse reactions

Reporting 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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no specific experience in the management of LENALIDOMIDE DRL overdose in patients. The dose limiting toxicity in these studies was essentially haematological. In the event of overdose, supportive care is advised.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A26. Cytostatic agents

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 proinflammatory 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).

<u>Cardiac Electrophysiology</u>

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 discontinuation of lenalidomide.

Metabolism

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

Excretion

Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy 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 Nacetyl-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.

Pharmacokinetics in children

No data are available.

Pharmacokinetics in the elderly

No data are available.

Pharmacokinetics in renal Impairment

The pharmacokinetics of lenalidomide were studied in patients 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 oral 25 mg dose of lenalidomide. Seven (7) healthy subjects of similar age with normal renal function (CLcr 83-145 mL/min) were administered a single oral 25 mg dose of lenalidomide. 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 healthy subjects.

Patients on haemodialysis had an approximately 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.

Pharmacokinetics in hepatic impairment:

No data are available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Croscarmellose sodium

Magnesium stearate

Mannitol

Microcrystalline cellulose

Povidone.

Capsule shell

FD & C blue 2 (E132) (LENALIDOMIDE DRL 10, LENALIDOMIDE DRL 15)

Gelatin

Iron oxide yellow (LENALIDOMIDE DRL 10)

Sodium lauryl sulphate

Titanium dioxide (E171)

Printing ink

Black iron oxide

Potassium hydroxide

Propylene glycol

Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

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

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

HDPE containers

The hard gelatin capsules are packed in white HDPE containers stoppered with white, plastic, child resistant caps, with a modified RH 20 % silica gel 1 g sachet cutform. The HDPE containers are packed into a cardboard unit carton.

LENALIDOMIDE DRL 15 / LENALIDOMIDE DRL 25

Pack size of 21 hard gelatin capsules.

LENALIDOMIDE DRL 5 / LENALIDOMIDE DRL 10

Pack size of 28 hard gelatin capsules.

Blister packs

Blister packs of 7 hard gelatin capsules (1 blister strip of 7 hard gelatin capsules each), 14 hard gelatin capsules (2 blister strips of 7 hard gelatin capsules each), 21 hard gelatin capsules (3 blister strips of 7 hard gelatin capsules each), or 28 hard gelatin capsules (4 blister strips of 7 hard gelatin capsules each) are available.

The hard gelatin capsules are packed into aluminium / aluminium foil blister strips composed of aluminium foil with heat seal laquer and cold formable aluminium foil. Each blister strip contains 7 hard gelatin capsules. The blister strip/s are packed into a cardboard unit carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The hard gelatin 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 product or waste material should be returned to the pharmacist for safe disposal in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

LENALIDOMIDE DRL 5: 52/26/0791

LENALIDOMIDE DRL 10: 52/26/0792

LENALIDOMIDE DRL 15: 52/26/0793

LENALIDOMIDE DRL 25: 52/26/0794

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 21 July 2020

10 DATE OF REVISION OF TEXT

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