**Applicant:** Aurogen SA (Pty) Ltd
**Product Name:** DATRENAL 2,5 mg/5 mg/7,5 mg/10 mg/15 mg/20 mg/ 25 mg;
**Dosage form and strength:** Each capsule contains 2,5 mg/ 5 mg/ 7,5 mg/10 mg/ 15 mg/20 mg/25 mg

**MODULE 1**
1.3.1.1

### 1.3.1.1 Approved Professional Information for Medicines for Human Use

**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

**DATRENAL 2,5 mg**

**DATRENAL 5 mg**

**DATRENAL 7,5 mg**

**DATRENAL 10 mg**

**DATRENAL 15 mg**

**DATRENAL 20 mg**

**DATRENAL 25 mg**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**DATRENAL 2,5 mg:**

Each capsule contains 2,5 mg lenalidomide.

Contains sugar: lactose anhydrous 20,0 mg

**DATRENAL 5 mg:**

Each capsule contains 5 mg lenalidomide.

Contains sugar: lactose anhydrous 40,0 mg

**DATRENAL 7,5 mg:**

Each capsule contains 7,5 mg lenalidomide.

Contains sugar: lactose anhydrous 60,0 mg

**DATRENAL 10 mg:**

Each capsule contains 10 mg lenalidomide.

Contains sugar: lactose anhydrous 80,0 mg

**DATRENAL 15 mg:**

Each capsule contains 15 mg lenalidomide.

Contains sugar: lactose anhydrous 120,0 mg

**DATRENAL 20 mg:**

Each capsule contains 20 mg lenalidomide.

Contains sugar: lactose anhydrous 160,0 mg

**DATRENAL 25 mg:**

Each capsule contains 25 mg lenalidomide.

Contains sugar: lactose anhydrous 200,0 mg

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

**DATRENAL 2,5 mg:**

Off-white to pale-yellow powder filled in green opaque capsules imprinted "L 2.5" on the cap in black ink and plain body, size 4, hard gelatine capsule.

**DATRENAL 5 mg:**

Off-white to pale-yellow powder filled in white opaque capsules imprinted "L 5" on the cap in black ink and plain body, size 2, hard gelatine capsule.

**DATRENAL 7,5 mg:**

Off-white to pale- yellow powder filled in white opaque capsules imprinted "L 7.5" on the cap in black ink and plain body, size 2, hard gelatine capsule.

**DATRENAL 10 mg:**

Off-white to pale-yellow powder filled in olive green and orange opaque capsules imprinted "L10" on the cap in black ink and plain body, size 0, hard gelatine capsule.

**DATRENAL 15 mg**

Off-white to pale-yellow powder filled in dark orange opaque capsules imprinted "L 15" on the cap in black ink and plain body, size 0, hard gelatine capsule.

**DATRENAL 20 mg**

Off-white to pale-yellow powder filled in orange opaque capsules imprinted "L 20" on the cap in black ink and plain body, size 0, hard gelatine capsule.

**DATRENAL 25 mg**

Off-white to pale-yellow powder filled in white opaque capsules imprinted "L 25" on the cap in black ink and plain body, size 0, hard gelatine capsule.

**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).**

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

DATRENAL is indicated for:

1. Myelodysplastic Syndromes (MDS):

DATRENAL 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.

2. Multiple Myeloma:

DATRENAL 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 DATRENAL is 10 mg given orally once a day on days 1-21 of repeating 28-day treatment cycles. |

Recommended dose adjustments during treatment and restart of treatment**:**

**Platelet counts**

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

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

| **If baseline ≥ 100 x $10^9$/L** | |
|---|---|
| When platelets | Recommended course |
| Fall to < 50 x $10^9$/L | Interrupt DATRENAL treatment |
| Return to ≥ 50 x $10^9$/L | Resume DATRENAL 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 DATRENAL treatment |
| If baseline ≥ 60 x $10^9$/Land returns to ≥ 50 x $10^9$/L | Resume DATRENAL at 5 mg once a day continuously in repeating 28 day cycles |
| If baseline < 60 x $10^9$/L and returns to ≥ 30 x $10^9$/ | Resume DATRENAL 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 DATRENAL treatment |
| Return to ≥ 30 x $10^9$/L (without signs of bleeding) | Resume DATRENAL 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 DATRENAL treatment |
| Return to ≥ 30 x $10^9$/L (without signs of bleeding) | Resume DATRENAL 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 DATRENAL treatment |
| Return to ≥ 1 x $10^9$/L | Resume DATRENAL 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 DATRENAL treatment |
| Return to ≥ 0,5 x $10^9$/L | Resume DATRENAL 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 DATRENAL treatment |
| Return to ≥ 0,5 x $10^9$/L | Resume DATRENAL at 5 mg once a day continuously in repeating 28 day cycles |

[+]Absolut 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 DATRENAL treatment |
| Return to ≥ 0,5 x $10^9$/L | Resume DATRENAL at 5 mg once every other day |

[+]Absolute neutrophil count

**Other Grade ¾ Toxicities**

For other Grade ¾ toxicities judged to be related to DATRENAL, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2.

**Discontinuation of DATRENAL**

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

DATRENAL 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 DATRENAL 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 DATRENAL.

**Platelet counts**

**Thrombocytopenia**

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

**Neutrophil counts (ANC)**

**Neutropenia**

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

**Other Grade ¾ Toxicities**

For other Grade ¾ toxicities judged to be related to DATRENAL, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2.

**Discontinuation of DATRENAL**

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

DATRENAL 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 DATRENAL 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 DATRENAL treatment and follow CBC weekly | Starting dose | 25 mg |
| Return to ≥ 30 x $10^9$/L | Resume DATRENAL at dose level – 1 | Dose level – 1 | 15 mg |
| For each subsequent drop below < 30 x $10^9$/L | Interrupt DATRENAL treatment | Dose level – 2 | 10 mg |
| | | Dose level – 3 | 5 mg |

| | | | |
|---|---|---|---|
| Return to ≥ 30 x $10^9$/L | Resume DATRENAL at the next lower dose level -2 or -3 for the indicated dose regimen.<br><br>Do not dose below the lowest DATRENAL dose level in the indicated dose regimen | | |

**Absolute neutrophil counts (ANC) Neutropenia**

| **When neutophils** | **Recommended course[a]** | **Dose levels** | **Previously treated Multiple Myeloma (combination with dexamethasone)**<br>**Days 1-21/28 day cycle** |
|---|---|---|---|
| Fall to < 0,5 x $10^9$/L | Interrupt DATRENAL treatment and follow CBC weekly | Starting dose | 25 mg |

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

**Other Grade ¾ Toxicities**

For other Grade ¾ toxicities judged to be related to DATRENAL, stop treatment and restart at next lower dose level when toxicity has resolved to ≤ Grade 2.

**Discontinuation of DATRENAL**

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

DATRENAL 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**

**Elderly patients:**

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

**Patients with renal impairment**

DATRENAL 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 DATRENAL 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 DATRENAL therapy, subsequent DATRENAL dose modification should be based on individual patient treatment tolerance, as described elsewhere in this section.

**Patients with hepatic impairment**

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

**Paediatric population:**

The safety and efficacy of DATRENAL in children under the age of 18 years has not been established.

**Method of administration**

DATRENAL should be taken orally at about the same time each day. The capsules should not be opened, broken, or chewed. DATRENAL 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

**DATRENAL** is contraindicated:

- Hypersensitivity to lenalidomide or any of the excipients (see section 6.1)
- In pregnancy and lactation.
- Women of childbearing potential, except when all of the conditions for pregnancy prevention have been met (see sections 4.4 and 4.6).

## 4.4. Special warnings and precautions for use

General:

***Pregnancy warning***

DATRENAL is contra-indicated during pregnancy.

DATRENAL 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 DATRENAL is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected. 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, DATRENAL 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 4 weeks after the end of treatment.

• Even if a woman of childbearing potential has amenorrhea she must follow all the advice on effective contraception.

• She should be capable of complying with effective contraceptive measures. She is informed and understands the potential consequences of pregnancy and the need to rapidly consult if there is a risk of pregnancy.

• She understands the need to commence the treatment as soon as DATRENAL 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 DATRENAL.

For male patients taking DATRENAL, 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 DATRENAL must meet the following conditions:

• Understand the expected teratogenic risk if engaged in sexual activity with a woman of childbearing potential.

• Understand the need for the use of a condom if engaged in sexual activity with a woman of childbearing potential.

The prescriber must ensure that for women of childbearing potential:

• The patient complies with the conditions of the Key Assist Risk Management Program, including confirmation that she has an adequate level of understanding.

• The patient has acknowledged the aforementioned conditions.

***Contraception***

Women of childbearing potential must use two reliable methods of contraception for 4 weeks before therapy, during therapy including dose interruptions, and until 4 weeks after DATRENAL 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 DATRENAL and dexamethasone, and in patients with myelodysplastic syndromes taking DATRENAL monotherapy, combined oral contraceptive pills are not recommended (see section 4.5). If a patient is currently using combined oral contraception the patient should switch to two of the effective methods listed above.

The risk of venous thromboembolism continues for 4-6 weeks after discontinuing combined oral contraception.

***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 DATRENAL 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 DATRENAL, 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 DATRENAL.

*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***

DATRENAL is present in human semen at extremely low levels during treatment and is undetectable in human semen 3 days after discontinuation of DATRENAL in the healthy subject (see section 5.2). As a precaution, and taking into account special populations with prolonged elimination time such as renal impairment, all male patients should use condoms throughout

treatment duration, during dose interruption and for 4 weeks after cessation of treatment if their partner is of childbearing potential and is not established on suitable contraception ( even if the male patient has undergone a vasectomy). Male patients taking DATRENAL should not donate sperm or semen during treatment including dose interruptions and for 4 weeks following the end of treatment.

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

***Educational materials***

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

<u>Other special warnings and precautions for use:</u>

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

• *Allergic Conditions*: Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal.

Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not

receive DATRENAL. DATRENAL interruption or discontinuation should be considered for Grade 2-3 skin rash. DATRENAL must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected, and should not be resumed following discontinuation for these reactions.

• *Tumour Lysis Syndrome and Tumour Flare Reaction*

Tumour lysis syndrome (TLS) and tumour flare reaction (TFR) have been observed in patients with Chronic Lymphocytic Leukemia (CLL), and in patients with other lymphomas, who were treated with lenalidomide. Fatal instances of TLS have been reported during treatment with lenalidomide. Patients at risk for TLS and TFR are those with high tumour burden prior to treatment. Caution should be practiced when introducing these patients to DATRENAL. These patients should be monitored closely, especially during the first cycle or dose-escalation, and appropriate precautions taken. There have been reports of TLS in patients with MM treated with lenalidomide.

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

• *Neutropenia and thrombocytopenia:* The major dose limiting toxicities of DATRENAL 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 DATRENAL treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2).

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

Co-administration of DATRENAL with other myelosuppressive agents 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 DATRENAL treatment and monthly thereafter to monitor for cytopenias. A dose reduction may be required (see section 4.2).

Multiple myeloma:

***Haematological toxicities***:

• Previously treated MM:

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

***Second Primary Malignancies***

• Previously treated MM

A numerical imbalance was observed in 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.

Optimal control of co-morbid conditions influencing thyroid function is recommended before start of treatment. Baseline and ongoing monitoring of thyroid function is recommended.

***Peripheral neuropathy***

Lenalidomide is structurally related to thalidomide, which is known to induce severe peripheral neuropathy. There was no increase in peripheral neuropathy observed with lenalidomide in combination with dexamethasone or melphalan and prednisone or lenalidomide monotherapy or with long term use of lenalidomide for the treatment of newly diagnosed multiple myeloma. The combination of lenalidomide with intravenous bortezomib and dexamethasone in multiple myeloma patients is associated with a higher frequency of peripheral neuropathy. The frequency was lower when bortezomib was administered subcutaneously.

***Cataract***

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

***Lactose intolerance***

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take DATRENAL.

### 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 DATRENAL is not likely to result in clinically relevant medicine interactions.

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

Coadministration of a single 25 mg dose of warfarin had no effect on the pharmacokinetics of DATRENAL. It is not known whether there is an interaction during concomitant treatment with dexamethasone. Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during treatment.

When digoxin 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 digoxin plasma levels is recommended during administration of DATRENAL.

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

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

*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 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 DATRENAL with dexamethasone (see section 4.4 and 4.8).**

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

Statins

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

### 4.6. Fertility, pregnancy and lactation

**Women of childbearing potential/Contraception in males and female**

DATRENAL 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 DATRENAL therapy including dose interruptions, and for 28 days following discontinuation of DATRENAL therapy, or continually abstain from sexual intercourse. There is an increased risk of VTE in patients with multiple myeloma taking DATRENAL and dexamethasone, and in patients with MDS taking DATRENAL 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 DATRENAL.

*Males*

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

***Criteria for women of non-childbearing potential***

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

• Age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year*

• Premature ovarian failure confirmed by a specialist gynaecologist

• Previous bilateral salpingo-oophorectomy, or hysterectomy

• XY genotype, Turner syndrome, uterine agenesis.

*Amenorrhoea following cancer therapy does not rule out childbearing potential.

**Pregnancy**

DATRENAL is contraindicated in pregnancy. If pregnancy occurs, DATRENAL should be immediately discontinued.

**Breastfeeding**

Breastfeeding is contraindicated during therapy with DATRENAL.

Fertility

No clinical data available.

### 4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive or use machines have been performed. DATRENAL may affect the ability to drive and use machines. Fatigue, dizziness, somnolence and blurred vision have been reported with the use of DATRENAL. Therefore, caution is recommended when driving or operating machines.

### 4.8. Undesirable effects

Frequency categories are expressed as: Frequent = very common and common; Less frequent = uncommon, rare and very rare; Frequency unknown = cannot be estimated and post-marketing.

#### a. *Tabulated list of adverse reactions*

| **System Organ Class/ Preferred Term** | **Frequency** | **All ADRs** | **Grade 3/4 ADRs** | **SADRs** |
|---|---|---|---|---|
| General disorders and administration site conditions | Frequent | Pyrexia, oedema (including peripheral), influenza like illness syndrome (including pyrexia, | Fatigue, pyrexia, asthenia, fall | |

| | | | | |
|---|---|---|---|---|
| | | cough, rhinitis, myalgia, musculoskeletal pain, pharyngitis, headache and rigors), fatigue, asthenia, chest pain | | |
| Gastrointestinal disorders | Frequent | Diarrhoea[@], vomiting[@], nausea[@], constipation, abdominal pain (including upper)[@], Dry mouth, dyspepsia | Diarrhoea@, nausea@, constipation, toothache | Diarrhoea[@] |
| 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, dysguesia, headache, lethargy, paraesthesia | Syncope, dizziness | Cerebrovascular accident[@] |
| Respiratory, thoracic and mediastinal disorders | Frequent | Dyspnoea, epistaxis | Respiratory distress[@] , bronchitis | |
| 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 subcutaneous tissue disorders | Frequent | Rash[+], pruritus, dry skin, hyperhidrosis | Rash, pruritus | |

| | | | | |
|---|---|---|---|---|
| Blood and lymphatic system disorders | Frequent | Neutropenia[%], thrombocytopenia[@], anaemia[@], leukopenia | Neutropenia[%], thrombocytopenia[@], anaemia[@], leukopenia, febrile neutropenia[%] | Anaemia[@], febrile neutropenia[%], neutropenia[%], thrombocytopenia[@] |
| Metabolism and nutrition disorders | Frequent | Decreased appetite, hypokalaemia, hypocalcaemia, dehydration, dypomagnesaemia, iron overload | Hypokalaemia, hypocalcaemia, hypophosphataemia, hyperglycaemia[%], decreased appetite | Hyperglycaemia[%] |
| 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 |
| Immune system disorders | Less frequent | Hypersensitivity | | |
| 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

**Post-marketing data:**

In addition to the above adverse reactions, the following table is derived from data gathered from post-marketing data.

| **System Organ Class/ Preferred Term** | **Frequency** | **All ADRs** | **Grade 3/4 ADRs** |
|---|---|---|---|
| Infections and infestations | Unknown | Viral infections, including herpes zoster and hepatitis B virus reactivation | Viral infections, including herpes zoster and hepatitis B virus reactivation |
| Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps) | Less frequent | | Tumour lysis syndrome |
| Blood and Lymphatic System Disorders | Unknown | Acquired haemophilia | |
| Immune system disorders | Unknown | Solid organ transplant rejection | |
| Endocrine disorders | Frequent | Hyperthyroidism | |
| Respiratory, Thoracic and Mediastinal Disorders | Unknown | | Interstitial pneumonitis |
| Gastrointestinal disorders | Unknown | | Pancreatitis, Gastrointestinal perforation (including |

| | | | |
|---|---|---|---|
| | | | diverticular, intestinal and large intestine perforations) |
| Hepatobiliary disorders | Unknown | Acute hepatic failure, Hepatitis toxic, Cytolytic hepatitis, Cholestatic hepatitis, Mixed cytolytic/cholestatic hepatitis | Acute hepatic failure, Hepatitis toxic |
| Skin and subcutaneous tissue disorders | Less frequent<br><br>Unknown | | Angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis<br><br>Leukocytoclastic vasculitis, Drug Reaction with Eosinophilia and Systemic Symptoms |

b. **Description of selected adverse reactions**

***Hepatic Disorders***

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

***Teratogenicity***

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

***Venous thromboembolism***

An increased risk of DVT and PE is associated with the use of the combination of lenalidomide with dexamethasone in patients with multiple myeloma, and to a lesser extent in patients treated with lenalidomide in combination with melphalan and prednisone or in patients with multiple myeloma, myelodysplastic syndromes and mantle cell lymphoma treated with lenalidomide monotherapy (see section 4.5).

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

***Myocardial infarction***

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

***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 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 lenalidomide (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***

• Multiple myeloma

Cases of AML have been observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide treatment in combination with melphalan or immediately following HDM/ASCT (see section 4.4). This increase was not observed in clinical trials of newly diagnosed multiple myeloma in patients taking lenalidomide in combination with dexamethasone compared to thalidomide in combination with melphalan and prednisone.

• 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). The estimated 2-year cumulative risk of progression to AML were 13,8 % in patients with an isolated Del (5q) abnormality compared to 17,3 % for patients with Del (5q) and one additional cytogenetic abnormality and 38,6 % in patients with a complex karyotype.

In a post-hoc analysis of a clinical trial of lenalidomide in myelodysplastic syndromes, the estimated 2-year rate of progression to AML was 27,5 % in patients with IHC-p53 positivity and 3,6

% in patients with IHCp53 negativity (p = 0,0038). In the patients with IHC-p53 positivity, a lower rate of progression to AML was observed amongst patients who achieved a transfusion independence (TI) response (11,1 %) compared to a non-responder (34,8 %).

***Rhabdomyolysis***

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

***Tumour flare reaction and tumour lysis syndrome***

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 lenalidomide. 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the ‘6.04

Adverse Drug Reactions Reporting Form', found under SAHPRA's publications:

https://www/sahpra.org.za/Publications/Index/8.

### 4.9. Overdose

There is no specific experience in the management of DATRENAL 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

Category and class: A32 Other - Immunomodulators

Pharmacological Classification: Other immunomodulators

Other immunosuppressants, ATC code: L04AX04

**Mechanism of action**

Lenalidomide is an oral immunomodulating agent with a pleiotropic mechanism of action involving direct tumouricidal activity, immunomodulation, pro-rythropoiesis, and anti-angiogenesis. Lenalidomide inhibits proliferation of certain aematopoietic 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).

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

**Distribution**

*In vitro* [$^{14}$C]-lenalidomide binding to plasma proteins is approximately 29 % in healthy volunteers and 23 % in multiple myeloma patients.
Lenalidomide is present in semen (< 0,01 % of the dose) after administration of 25 mg/day and the substance is undetectable in semen 3 days after discontinuation of lenalidomide.

**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 isexcreted as lenalidomide, almost exclusively via the urinary route. Hydroxylenalidomide 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.

**Special Populations**

**Renal impairment**

The pharmacokinetics of lenalidomide were studied in patients with renal impairment due to nonmalignant 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

DATRENAL capsules contain the following inactive ingredients:

Lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate

Capsule shell composition:

DATRENAL 2,5 mg: Gelatine, titanium dioxide, iron oxide yellow, FD &C blue 2

DATRENAL 5 mg: Gelatine, titanium dioxide

DATRENAL 2,5 mg: Gelatine, titanium dioxide, iron oxide yellow, FD &C blue 2

DATRENAL 7,5 mg: Gelatine, titanium dioxide

DATRENAL 10 mg: Gelatine, titanium dioxide, iron oxide yellow, iron oxide red, FD &C blue 2

DATRENAL 15 mg: Gelatine, titanium dioxide, iron oxide red

DATRENAL 20 mg: Gelatine, titanium dioxide, iron oxide yellow, iron oxide red

DATRENAL 25 mg: Gelatine, titanium dioxide

Composition of printing ink: Shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, strong ammonia solution, black iron oxide, potassium hydroxide.

### 6.2. Incompatibilities

Not applicable

### 6.3. Shelf life

24 months

### 6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

**KEEP OUT OF REACH OF CHILDREN.**

### 6.5. Nature and contents of container

DATRENAL Capsules 2,5 mg, 5 mg, 7,5 mg, 10 mg, 15 mg, 20 mg and 25 mg are packed in the clear PVC film - aluminium foil blister pack. The blisters are further packed in pre-printed cartons with package leaflet.

Pack sizes:

3 x blister of 7 capsules

### 6.6. Special precautions for disposal and other handling

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

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

## 8. REGISTRATION NUMBER

**DATRENAL 2,5 MG: 56/32/0511**

**DATRENAL 5 MG: 56/32/0512**

**DATRENAL 7,5 MG: 56/32/0513**

**DATRENAL 10 MG: 56/32/0514**

**DATRENAL 15 MG: 56/32/0515**

**DATRENAL 20 MG: 56/32/0516**

**DATRENAL 25 MG: 56/32/0517**

## 9. DATE OF FIRST AUTHORISATION

08 AUGUST 2023