**PROFESSIONAL INFORMATION – CLEAN AUGUST 2020**

**SCHEDULING STATUS**

S5

**1. NAME OF THE MEDICINE**

**PREGABALIN MYLAN 25 mg Capsules**

**PREGABALIN MYLAN 75 mg Capsules**

**PREGABALIN MYLAN 150 mg Capsules**

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each hard capsule contains 25 mg, 75 mg, or 150 mg of pregabalin

Sugar free.

For full list of excipients, see section 6.1

**3. PHARMACEUTICAL FORM**

Capsules, hard

**PREGABALIN MYLAN 25 mg:** Size 4, hard gelatin capsules with a white opaque cap and a white opaque body printed in black ink with “MYLAN” over ‘PG 25’ on the cap and body filled with white to off-white powder. Capsule length 14,2 mm

**PREGABALIN MYLAN 75 mg:** Size 4, hard gelatin capsules with a red brown opaque cap and white opaque body printed in black in with “MYLAN” over ‘PG 75’ on the cap and body filled with white to off-white powder. Capsule length 14,2 mm

**PREGABALIN MYLAN 150 mg:** Size 2, hard gelatin capsules with a white opaque cap and white opaque body printed in black ink with “MYLAN” over ‘PG 150’ on the cap and body filled with white to off-white powder. Capsule length 17,9 mm

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**PREGABALIN MYLAN** capsules are indicated for the treatment of adult patients with neuropathic pain due to Herpes zoster infections and diabetes.

### 4.2 Posology and method of administration

**Posology:**

The recommended starting dose for **PREGABALIN MYLAN** is 75 mg twice daily (150 mg/day), with or without food. Based on individual patient response and tolerability, the dose may be increased to 150 mg twice daily after an interval of 3 to 7 days. In accordance with current clinical practice, if **PREGABALIN MYLAN** has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

**Special Populations**

**Patients with renal impairment:**

**PREGABALIN MYLAN** is eliminated from the systemic circulation primarily by renal excretion as unchanged pregabalin. As **PREGABALIN MYLAN** clearance is directly proportional to creatinine clearance (see section 5.2), dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

$$CL_{CR}(ml/min) = \left[ \frac{1.23 \times [140 - age\ (years)] \times weight\ (kg)}{serum\ creatinine\ (\mu mol/l)} \right] (\times\ 0.85\ for\ female\ patients)$$

| **Table 1: PREGABALIN MYLAN dosage adjustment based on renal function [1]** | | | |
|---|---|---|---|
| **Creatinine clearance ($CL_{CR}$) (ml/min)** | **Total PREGABALIN MYLAN daily dose*** | | **Dose regimen** |
| | **Starting dose (mg/day)** | **Maximum dose (mg/day)** | |
| ≥ 60 | 150 | 300 | BD |
| 30 - 60 | 75 | 150 | OD or BD |
| 15 - 30 | 25 - 50 | 75 | OD or BD |
| < 15 | 25 | 25 - 50 | OD |
| Supplementary dosage following haemodialysis (mg) | | | |
| | 25 | 50 | Single dose' |

BD = Two divided doses

OD = Once daily

* Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose

' Supplementary dose is a single additional dose

**PREGABALIN MYLAN** is removed effectively from plasma by haemodialysis (50 % of medicine in 4 hours). For patients receiving haemodialysis, the **PREGABALIN MYLAN** daily dose should be adjusted based on renal function. In addition to the daily

dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

***Use in patients with hepatic impairment:***

No dosage adjustment is required for patients with hepatic impairment (see section 5.2).

***Paediatric patients:***

The safety and effectiveness of **PREGABALIN MYLAN** in patients below the age of 18 years with neuropathic pain has not been established.

***Use in the elderly (over 65 years of age):***

No dosage adjustment is necessary for elderly patients unless their renal function is compromised, see Table 1.

**Method of administration**

**PREGABALIN MYLAN** is given orally with or without food.

**4.3 Contraindications**

Known hypersensitivity to pregabalin or to any of the excipients of **PREGABALIN MYLAN** (see section 6.1).

**4.4 Special warnings and precautions for use**

***Diabetic patients***

Diabetic patients who gain weight on **PREGABALIN MYLAN** treatment may need to adjust hypoglycaemic medicines.

***Hypersensitivity reactions***

**PREGABALIN MYLAN** should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

***Dizziness, somnolence, loss of consciousness, confusion, and mental impairment***

**PREGABALIN MYLAN** treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have been reports of loss of consciousness, confusion and mental impairment. Patients should be advised to exercise caution until they are familiar with the potential effects of **PREGABALIN MYLAN.**

***Vision-related effects***

Visual adverse reactions have been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of **PREGABALIN MYLAN** may result in resolution or improvement of these visual symptoms.

***Renal failure***

Renal failure has been reported and discontinuation of pregabalin, as in **PREGABALIN MYLAN**, did show reversibility of this adverse reaction.

***Withdrawal symptoms***

After discontinuation of short-term and long-term treatment with pregabalin, as in **PREGABALIN MYLAN**, withdrawal symptoms have been observed. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

Convulsions, including status epilepticus and grand mal convulsions, may occur during **PREGABALIN MYLAN** use or shortly after discontinuing.

Discontinuation of long-term treatment of pregabalin, as in **PREGABALIN MYLAN**, data suggest that the incidence and severity of withdrawal symptoms may be dose related.

***Congestive heart failure***

Congestive heart failure has been reported. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. **PREGABALIN MYLAN** should be used with caution in these patients. Discontinuation of **PREGABALIN MYLAN** may resolve the reaction.

***Suicidal ideation and behaviour***

Suicidal ideation and behaviour have been reported in patients treated with Gabapentinoids such as pregabalin in **PREGABALIN MYLAN** in several indications. Therefore, patients should be monitored for signs of suicidal ideation and behaviours

and appropriate treatment should be considered. Patients and caregivers should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

***Reduced lower gastrointestinal tract function***

Reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) has been reported when pregabalin was co-administered with medicines that have the potential to produce constipation, such as opioid analgesics. When **PREGABALIN MYLAN** and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and the elderly).

***Concomitant use with opioids***

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression (see section 4.5). In a case control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone. This increased risk was observed at low doses of pregabalin (≤ 300 mg) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg).

***Misuse, abuse potential or dependence***

Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of **PREGABALIN MYLAN** misuse, abuse or dependence (development of tolerance, dose escalation, intentional overdose, drug-seeking behaviour have been reported).

***Encephalopathy***

Encephalopathy has been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

**4.5 Interaction with other medicines and other forms of interaction**

Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (< 2 % of a dose recovered in urine as metabolites), does not inhibit medicine metabolism *in vitro*, and is not bound to plasma proteins, **PREGABALIN MYLAN** is unlikely to produce, or be subject to, pharmacokinetic interactions.

***In vivo studies and population pharmacokinetic analysis***

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between **PREGABALIN MYLAN** and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. In addition, population pharmacokinetic analysis indicated that the 3 commonly used medicine classes, oral antidiabetics, diuretics and insulin, and the commonly used anti-epileptic medicines, phenytoin, carbamazepine, valproic acid, lamotrigine, phenobarbitone, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Similarly, these analyses indicated that **PREGABALIN MYLAN** had no clinically significant effect on the clearance of phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate and phenobarbitone.

***Oral contraceptives, norethisterone and/or ethinyl oestradiol***

Co-administration of **PREGABALIN MYLAN** with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either medicine.

***Central nervous system influencing medicines***

Multiple oral doses of **PREGABALIN MYLAN** co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. **PREGABALIN MYLAN** appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. **PREGABALIN MYLAN** may potentiate the effects of ethanol and lorazepam.

In the post marketing experience, there are reports of respiratory failure and coma in patients taking **PREGABALIN MYLAN** and other CNS depressant medications.

***Interactions and the elderly***

No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

There are no adequate data on the use of **PREGABALIN MYLAN** in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown. Therefore, **PREGABALIN MYLAN** should not be used during pregnancy.

**Breast-feeding**

Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on new-borns/infants is unknown. Therefore, breastfeeding is not recommended during treatment with **PREGABALIN MYLAN**.

**Fertility**

There are no clinical data on the effects of pregabalin on female fertility.

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

**PREGABALIN MYLAN** frequently causes dizziness and somnolence. Head and body injuries and road traffic incidents have also been reported with pregabalin, as contained in **PREGABALIN MYLAN**. Therefore, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicine affects their ability to perform these activities.

### 4.8 Undesirable effects

**a) Summary of adverse effects**

The most frequently reported adverse reactions were dizziness and somnolence. The most frequent adverse reactions resulting in discontinuation from pregabalin treatment are dizziness and somnolence.

In the table below the adverse reactions are listed by system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Additional reactions reported from post marketing experience are also included and listed according to frequency.

## b) Tabulated summary of adverse reactions

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Infections and infestations: | Frequent | Nasopharyngitis |
| Blood and the lymphatic system disorders | Less frequent | Neutropenia |
| Immune system disorders | Less frequent | Hypersensitivity, angioedema, allergic reaction |
| Metabolism and nutrition disorders | Frequent | Increased appetite |
| | Less frequent | Anorexia, hypoglycaemia |
| Psychiatric disorders | Frequent | Euphoric mood, confusion, irritability, disorientation, insomnia, decreased libido |
| | Less frequent | Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, increased libido, anorgasmia, apathy, disinhibition |

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| | Unknown frequency | Suicidal ideation and behaviour |
| Nervous system disorders | Frequent | Dizziness, somnolence, headache, ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy |
| | Less frequent | Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise, convulsions, parosmia, hypokinesia, dysgraphia |
| Eye disorders | Frequent | Blurred vision, diplopia |

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| | Less frequent | Peripheral vision loss, visual disturbance, eye swelling, visual field defect, reduced visual acuity, eye pain, asthenopia, photopsia, dry eye, increased lacrimation, eye irritation, vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness |
| Ear and labyrinth disorders | Frequent | Vertigo |
| | Less frequent | Hyperacusis |
| Cardiac disorders | Less frequent | Tachycardia, first degree atrioventricular block, sinus bradycardia, congestive heart failure, QT prolongation, sinus tachycardia, sinus dysrhythmi |
| Vascular disorders | Less frequent | Hypotension, hypertension, hot flushes, flushing, peripheral coldness |

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Respiratory, thoracic and mediastinal disorders: | Less frequent | Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness, pulmonary oedema, throat tightness |
| Gastrointestinal disorders: | Frequent | Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth |
| | Less frequent | Gastro-oesophageal reflux disease, salivary hypersecretion, oral hypoaesthesia, ascites, pancreatitis, swollen tongue, dysphagia |
| Hepatobiliary disorders | Less frequent | Elevated liver enzymes*, jaundice, hepatic failure, hepatitis |
| Skin and subcutaneous tissue disorders: | Less frequent | Papular rash, urticaria, hyperhidrosis, pruritus, Stevens Johnson syndrome, cold sweat |
| Musculoskeletal and connective tissue disorders: | Frequent | Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm |
| | Less frequent | Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness, rhabdomyolysis |

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Renal and urinary disorders: | Less frequent | Urinary incontinence, dysuria, renal failure, oliguria, urinary retention |
| Reproductive system and breast disorders | Frequent | Erectile dysfunction |
| | Less frequent | Sexual dysfunction, delayed ejaculation, dysmenorrhoea, breast pain, amenorrhoea, breast discharge, breast enlargement, gynaecomastia |
| General disorders and administration site conditions: | Frequent | Peripheral oedema, oedema, abnormal gait, fall, feeling drunk, feeling abnormal, fatigue |
| | Less frequent | Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, astheni |
| Investigations: | Frequent | Increased weight (2) |
| | Less frequent | Increased blood creatine phosphokinase, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood glucose, |

| **MedDRA system organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| | | decreased platelet count, increased blood creatinine, decreased blood potassium, decreased weight, decreased white blood cell count |

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

**c. Description of selected adverse reactions**

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose related.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to

SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

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

### 4.9 Overdose

In the post marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported. In rare occasions, cases of coma have been reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and Class: A 2.5 Central nervous sytem depressants – Anticonvulsants: including antiepileptics.

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics ATC code: N03AX16

The active substance, pregabalin, is a gamma-aminobutyric acid (GABA) analogue ((S)-3 (aminomethyl)-5-methylhexanoic acid).

Pregabalin binds to an auxiliary subunit ($\alpha_2$-σ protein) of voltage-gated calcium channels in the central nervous system, displacing (3H)-gabapentin.

Two lines of evidence indicate that binding of pregabalin to the $\alpha_2$-σ site is required for analgesic activity in animal models: (1) Studies with the inactive R-enantiomer and other structural derivatives of pregabalin and (2) Studies of pregabalin in mutant mice with defective binding to the $\alpha_2$-σ protein. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

Pregabalin does not interact with either GABAA or GABAB receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of GABA uptake or degradation. (1)

Pregabalin prevents pain-related behaviours in animal models of neuropathic and post-surgical pain, including hyperalgesia and allodynia.

### 5.2 Pharmacokinetic properties

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers and patients with chronic pain.

### Absorption

Pregabalin is absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90 % and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in $C_{max}$ by approximately 25 – 30 % and a delay in $T_{max}$ to

approximately 2,5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

**Distribution**

In pre-clinical studies, pregabalin has been shown to readily cross the blood brain barrier in mice, rats and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0,56 L/kg. Pregabalin is not bound to plasma proteins.

**Metabolism**

Pregabalin undergoes negligible metabolism in humans. Following a dose of radio-labelled pregabalin, approximately 98 % of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0,9 % of the dose. In pre-clinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

**Elimination**

Pregabalin is eliminated unchanged from the systemic circulation primarily by renal excretion.

Pregabalin mean elimination half-life is 6,3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see "Pharmacokinetics in special patient groups – Renal impairment"). Dosage adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2).

**Linearity/non-linearity**

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (< 20 %). Multiple dose pharmacokinetics are predictable from single-dose data.

**Special Populations:**

***Renal impairment:***

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4-hour haemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50 %). Because renal elimination is the major elimination pathway, dosage reduction in patients with renal impairment and dosage supplementation following haemodialysis is necessary (see section 4.2).

***Elderly (over 65 years of age):***

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function (see section 4.2).

***Gender***

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

**6. PHARMACEUTICAL PARTICULARS**

### 6.1 List of excipients

*Capsule fill:*

Corn starch

Low-substituted hydroxypropyl cellulose

Purified talc

*Capsule shell:*

Black S-1-17822/17823 printing ink {ammonium hydroxide (E527), isopropyl alcohol, iron oxide black (E172), n-butyl alcohol, propylene glycol (E1520), shellac}

gelatin

titanium dioxide

purified water

*75 mg capsule shell includes:*

red iron oxide (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store at or below 25 ˚C.

Keep the container well closed.

### 6.5 Nature and contents of container

**PREGABALIN MYLAN** is packed in a HDPE bottle pack (marketable pack) comprising of a round wide mouth white HDPE bottle with white opaque polypropylene (PP) screw cap with aluminium induction sealing wad.

Pack size of 60 capsules.

* Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

No special precautions are required.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

MYLAN (PTY) LTD

4 Brewery Street, Isando, 1600

Republic of South Africa

## 8. REGISTRATION NUMBERS

**PREGABALIN MYLAN 25 mg:** 46/2.5/0219

**PREGABALIN MYLAN 75 mg:** 46/2.5/0220

**PREGABALIN MYLAN 150 mg:** 46/2.5/0221

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 October 2020

## 10 DATE OF REVISION OF THE TEXT