PACKAGE INSERT

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

PREGABALIN IVAX 25 (capsule)

PREGABALIN IVAX 50 (capsule)

PREGABALIN IVAX 75 (capsule)

PREGABALIN IVAX 150 (capsule)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each hard capsule contains 25 mg, 50 mg, 75 mg, or 150 mg of pregabalin.

Contains sugar (mannitol).

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

3. PHARMACEUTICAL FORM:

PREGABALIN IVAX hard gelatin capsules contain a white to off-white, granulated powder.

PREGABALIN IVAX 25: Ivory opaque hard gelatin capsule imprinted in black with '25' on the capsule body.

PREGABALIN IVAX 50: Ivory opaque hard gelatin capsule with the capsule cap imprinted with a radial black band and the capsule body imprinted in black with '50' and a radial black band.

PREGABALIN IVAX 75: Opaque hard gelatin capsule with a pink cap and ivory body imprinted in black with '75'.

PREGABALIN IVAX 150: Ivory opaque hard gelatin capsule imprinted in black with '150' on the capsule body.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

Neuropathic pain:

PREGABALIN IVAX is indicated for the treatment of adult patients with neuropathic pain due to Herpes zoster infections and diabetes.

4.2 Posology and method of administration:

The recommended starting dose for **PREGABALIN IVAX** 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 IVAX** has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Patients with renal impairment:

PREGABALIN IVAX is eliminated unchanged from the systemic circulation primarily by renal excretion. As **PREGABALIN IVAX** clearance is directly proportional to creatinine clearance (see **section 5.2 - *Pharmacokinetics in Special Patient Groups – Renal impairment***), dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}), as indicated in **Table 1** determined using the following formula:

$$CL_{cr}\ (ml/min) = \frac{(140 - age) \times weight\ (kg)}{0{,}82 \times Serum\ creatinine\ (\mu mol/l)}$$

*For females multiply the CL_{cr} by 0,85

PREGABALIN IVAX is removed effectively from plasma by haemodialysis (50 % of pregabalin in 4 hours). For patients receiving haemodialysis, the daily dose of **PREGABALIN IVAX** 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 (refer to **Table 1**).

TABLE 1: PREGABALIN IVAX DOSAGE ADJUSTMENT BASED ON RENAL FUNCTION

CREATININE CLEARANCE (Cl_{cr}) (ml/min)	**TOTAL PREGABALIN IVAX DAILY DOSE***		**DOSE REGIMEN**
	Starting dose (mg/day)	**Maximum dose (mg/day)**	
≥ 60	150	300	BD
30 to 60	75	150	OD or BD
15 to 30	25 to 50	75	OD or BD
< 15	25	25 to 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

Use in patients with hepatic impairment:

No dosage adjustments are required for patients with hepatic impairment (see **section 5.2** - ***Pharmacokinetics in Special Patient Groups – Hepatic Impairment***).

Use in children:

The safety and effectiveness of **PREGABALIN IVAX** 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, refer to **Table 1**.

Method of administration:

PREGABALIN IVAX is given orally with or without food.

4.3 Contraindications:

PREGABALIN IVAX is contraindicated in patients who are hypersensitive to pregabalin or to any of the excipients.

4.4 Special warnings and precautions for use:

Hypersensitivity reactions:

There have been reports of hypersensitivity reactions, including cases of angioedema and urticaria.

PREGABALIN IVAX should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur (see **section 4.8**).

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

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of **PREGABALIN IVAX** (see **section 4.8**).

Use with anti-depressant medicines:

When **PREGABALIN IVAX** is used in combination with anti-depressant medicines, respiratory failure has occurred.

Withdrawal symptoms:

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

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

During discontinuation of long-term treatment with **PREGABALIN IVAX**, the incidence and severity of withdrawal symptoms may be dose-related.

Renal failure:

Renal failure may occur with **PREGABALIN IVAX**. Improved renal function was reported following dose reduction or discontinuation of **PREGABALIN IVAX**.

Congestive heart failure:

There have been post-marketing reports of congestive heart failure or deterioration of heart failure in some patients receiving **PREGABALIN IVAX**. These are mostly seen in elderly cardiovascular compromised patients during **PREGABALIN IVAX** treatment. Therefore **PREGABALIN IVAX** should be used with caution in patients with congestive heart failure (see **section 4.8**). Discontinuation of **PREGABALIN IVAX** may resolve the reaction.

Diabetic patients:

In accordance with current clinical practice, some diabetic patients who gain weight on **PREGABALIN IVAX** treatment may need to adjust hypoglycaemic medicines.

Vision-related effects:

There have been post-marketing reports of visual adverse reactions including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of **PREGABALIN IVAX** may result in resolution or improvement of these visual symptoms.

Treatment of central neuropathic pain due to spinal cord injury:

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicines (e.g. anti-spasticity medicines) needed for this condition. This should therefore be considered when prescribing **PREGABALIN IVAX** in this condition.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines in several indications. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Reduced lower gastrointestinal tract function:

There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medicines that have the potential to produce constipation, such as opioid analgesics. When **PREGABALIN IVAX** and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and the elderly).

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 misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported).

Encephalopathy:

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

Respiratory depression:

There have been reports of severe respiratory depression in relation to **PREGABALIN IVAX** use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients (see **section 4.2**).

Mannitol:

PREGABALIN IVAX contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction:

Since **PREGABALIN IVAX** is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans, does not inhibit medicine metabolism *in vitro* and is not bound to plasma proteins, **PREGABALIN IVAX** is unlikely to produce, or be subject to, pharmacokinetic interactions.

No pharmacokinetic interactions were observed between **PREGABALIN IVAX** and the following medicines: phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone, ethanol, oral anti-diabetics, diuretics, insulin and anti-epileptic medicines (such as phenytoin, carbamazepine, phenobarbitone, tiagabine and topiramate), oral contraceptives (e.g. norethisterone and/or ethinyl oestradiol).

PREGABALIN IVAX appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone and may potentiate the effects of ethanol and lorazepam.

In patients taking **PREGABALIN IVAX** and other central nervous system (CNS) depressant medicines, there have been post-marketing reports of respiratory failure and coma.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

PREGABALIN IVAX should not be used during pregnancy since safety and efficacy has not been established, therefore effective contraception must be used in women of childbearing potential.

Breastfeeding:

PREGABALIN IVAX is excreted in breast milk therefore breastfeeding is not recommended, since the effects on newborns/infants are unknown.

4.7 Effects on the ability to drive and use machines:

PREGABALIN IVAX frequently causes dizziness and somnolence. Therefore, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether **PREGABALIN IVAX** affects their ability to perform these activities.

4.8 Undesirable effects:

The most frequently reported adverse reactions are dizziness and somnolence.

Infections and infestations:

Frequent: Nasopharyngitis

Immune system disorders:

Frequency unknown: Hypersensitivity reactions, angioedema, allergic reaction

Blood and lymphatic system disorders:

Less frequent: Neutropenia

Metabolism and nutrition disorders:

Frequent: Increased appetite

Less frequent: Anorexia, hypoglycaemia

Psychiatric disorders:

Frequent: Euphoric mood, confusion, decreased libido, irritability, disorientation, insomnia

Less frequent: Depersonalisation, anorgasmia, restlessness, depression, agitation, mood swings, insomnia exacerbated, depressed mood, word finding difficulty, hallucination, abnormal dreams, libido increased, panic attack, apathy, disinhibition, elevated mood, aggression

Nervous system disorders:

Frequent: Dizziness, somnolence, ataxia, disturbance in attention, abnormal co-ordination, memory impairment, tremor, dysarthria, paraesthesia, headache, amnesia, hypoaesthesia, balance disorder, lethargy

Less frequent: Cognitive disorder, visual field defect, nystagmus, speech disorder, myoclonus, hyporeflexia, dyskinesia, psychomotor hyperactivity, postural dizziness, hyperaesthesia, ageusia, burning sensation, intention tremor, stupor, syncope, hypokinesia, parosmia, dysgraphia, loss of consciousness, nystagmus, mental impairment, malaise, convulsions, parkinsonism

Frequency unknown: Reversible paralysis

Eye disorders:

Frequent: Vision blurred, diplopia

Less frequent: Visual disturbance, dry eye, eye swelling, reduced visual acuity, eye pain, asthenopia, increased lacrimation, photopsia, eye irritation, mydriasis, oscillopsia, altered visual depth perception, peripheral vision loss, strabismus, visual brightness, keratitis

Ear and labyrinth disorders:

Frequent: Vertigo

Less frequent: Hyperacusis

Cardiac disorders:

Less frequent: Tachycardia, atrioventricular block first degree, sinus tachycardia, sinus dysrhythmia, sinus bradycardia, congestive heart failure, QT prolongation

Vascular disorders:

Less frequent: Flushing, hot flushes, hypotension, peripheral coldness, hypertension

Respiratory, thoracic and mediastinal disorders:

Less frequent: Dyspnoea, nasal dryness, cough, nasal congestion, epistaxis, rhinitis, snoring, throat tightness, pulmonary oedema

Frequency unknown: Respiratory depression

Gastrointestinal disorders:

Frequent: Dry mouth, constipation, vomiting, flatulence, nausea, diarrhoea, abdominal distension

Less frequent: Salivary hypersecretion, gastro-oesophageal reflux disease, oral hypoaesthesia, ascites, dysphagia, pancreatitis, swollen tongue

Hepatobiliary disorders:

Less frequent: Elevated liver enzymes, jaundice, hepatic failure, hepatitis

Skin and subcutaneous tissue disorders:

Less frequent: Sweating, rash papular, cold sweat, urticaria, face swelling, Stevens-Johnson syndrome, pruritus

Musculoskeletal and connective tissue disorders:

Frequent: Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm

Less frequent: Muscle twitching, joint swelling, myalgia, muscle stiffness, neck pain, rhabdomyolysis

Renal and urinary disorders:

Less frequent: Dysuria, urinary incontinence, oliguria, renal failure, urinary retention

Reproductive system and breast disorders:

Frequent: Erectile dysfunction

Less frequent: Ejaculation delayed, sexual dysfunction, amenorrhoea, breast pain, breast discharge, dysmenorrhoea, breast hypertrophy, gynaecomastia

General disorders and administration site conditions:

Frequent: Fatigue, peripheral oedema, feeling drunk, oedema, abnormal gait, fall, feeling abnormal

Less frequent: Asthenia, thirst, chest tightness, exacerbated pain, anasarca, pyrexia, rigors, face oedema,

chills, generalised oedema

Investigations:

Frequent: Increased weight

Less frequent: Increased alanine aminotransferase, increased blood creatine phosphokinase, increased aspartate aminotransferase, decreased platelet count, increased blood glucose, increased blood creatinine, decreased blood potassium, decreased weight, decreased white blood cell count

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after registration of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine.

Healthcare 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:

Post-marketing reports of pregabalin overdose included affective disorder, somnolence, confusional state, depression, agitation, restlessness, seizures and coma.

Treatment of **PREGABALIN IVAX** overdose should include general supportive measures and may include haemodialysis if necessary (see **section 4.2**).

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 2.5 Central nervous system depressants – Anticonvulsants, including 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 (α_2-δ protein) of voltage-gated calcium channels in the central nervous system and displaces [^{3}H]-gabapentin.

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 $GABA_A$ or $GABA_B$ receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of GABA uptake or degradation.

5.2 Pharmacokinetic properties:

Absorption:

Pregabalin is absorbed after oral administration in the fasted state. Peak plasma concentrations are achieved within 1 hour and is independent of dose. Pregabalin oral bioavailability is estimated to be ≥ 90 % and is independent of dose. After repeated administration, steady state is achieved within 24 to 48 hours.

Distribution:

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. About 98 % of the unchanged pregabalin is recovered in the urine.

Elimination:

Pregabalin is eliminated primarily unchanged by renal excretion. Pregabalin has a mean elimination half-life of 6,3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see **section 5.2** - ***Pharmacokinetics in Special Patient Groups - Renal impairment***). Dosage adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see **section 4.2 - Table 1**).

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. Therefore routine monitoring of plasma concentrations of pregabalin is not necessary.

Pharmacokinetics in special patient groups:

Renal impairment:

Pregabalin clearance is directly proportional to creatinine clearance. 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, a dosage reduction in patients with renal impairment and dosage supplementation following haemodialysis is necessary (see **section 4.2 - Table 1**).

Hepatic impairment:

Since pregabalin does not undergo significant metabolism and is excreted unchanged in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

Elderly (over 65 years of age):

Pregabalin clearance tends to decrease as age increases. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of the dose of pregabalin may be required in patients who have age related compromised renal function (see **section 4.2 - Table 1**).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Maize starch, mannitol, talc.

Capsule shell contains: colourants (titanium dioxide, yellow iron oxide and red iron oxide), gelatin.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

2 years.

6.4 Special precautions for storage:

Store at or below 25 °C in the original container.

Keep blisters in the outer carton until required for use. Keep bottles well closed.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container:

- **PREGABALIN IVAX 25, 50, 75 & 150** are packed in PVC/aluminium blisters. The blister consists of a silver/grey aluminum foil with a transparent, colourless PVC foil. Blisters are contained in an outer carton.

  Pack size 14: Each carton contains 1 blister strip with 14 capsules per blister.

  Pack size 56: Each carton contains 4 blister strips with 14 capsules per blister.

  Pack size 60: Each carton contains 6 blister strips with 10 capsules per blister.

  Pack size 100: Each carton contains 10 blister strips with 10 capsules per blister.
- **PREGABALIN IVAX 75** is packed in a white, high density polyethylene (HDPE) 150 ml bottle, with a white polypropylene closure with an inner seal. Pack size: 200 capsules.
- **PREGABALIN IVAX 150** is packed in a white, high density polyethylene (HDPE) 300 ml bottle, with a white polypropylene closure with an inner seal. Pack size: 200 capsules.

Not all pack sizes are marketed.

6.6 Special precautions for disposal and other handling:

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

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park,

Magwa Crescent West,

Waterfall City, Midrand,

Gauteng,

2090,

South Africa

Tel: (011) 055 0200

8. REGISTRATION NUMBERS:

PREGABALIN IVAX 25: 46/2.5/0772

PREGABALIN IVAX 50: 46/2.5/0773

PREGABALIN IVAX 75: 46/2.5/0774

PREGABALIN IVAX 150: 46/2.5/0775

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

23 November 2017

10. DATE OF REVISION OF THE TEXT:

29 March 2021