PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

TIMIRIL 25 (Capsules)

TIMIRIL 50 (Capsules)

TIMIRIL 75 (Capsules)

TIMIRIL 100 (Capsules)

TIMIRIL 150 (Capsules)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TIMIRIL 25

Each capsule contains 25 mg pregabalin.

TIMIRIL 50

Each capsule contains 50 mg pregabalin.

TIMIRIL 75

Each capsule contains 75 mg pregabalin.

TIMIRIL 100

Each capsule contains 100 mg pregabalin.

TIMIRIL 150

Each capsule contains 150 mg pregabalin.

For full list of excipients, see section 6.1.

Sugar free.

3 PHARMACEUTICAL FORM

Capsules.

TIMIRIL 25

Hard gelatin capsule with a white coloured cap and white coloured body, printed with "S" on cap and "466" on body with black ink containing a white to off-white crystalline powder.

TIMIRIL 50

Hard gelatin capsule with a white coloured cap and white coloured body, printed with "S" on cap and "467" on body with black ink containing a white to off-white crystalline powder.

TIMIRIL 75

Hard gelatin capsule with an orange coloured cap and white coloured body, printed with "S" on cap and "468" on body with black ink containing a white to off-white crystalline powder.

TIMIRIL 100

Hard gelatin capsule with an orange coloured cap and orange coloured body, printed with "S" on cap and "469" on body with black ink containing a white to off-white crystalline powder.

TIMIRIL 150

Hard gelatin capsule with a white coloured cap and white coloured body, printed with "S" on cap and "470" on body with black ink containing a white to off-white crystalline powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TIMIRIL is indicated for the treatment of neuropathic pain due to Herpes Zoster infection and diabetes in adult patients.

4.2 Posology and method of administration

Posology

The recommended starting dose is 75 mg twice daily (150 mg/day). 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.

Discontinuation of Pregabalin

In accordance with current clinical practice, if **TIMIRIL** must be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Special populations

Patients with renal impairment:

TIMIRIL is eliminated unchanged from the systemic circulation primarily by renal excretion. As **TIMIRIL** 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 (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

TIMIRIL is removed effectively from plasma by haemodialysis (50 % of pregabalin in 4 hours). For patients receiving haemodialysis, the **TIMIRIL** 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).

Table 1. TIMIRIL dose adjustment based on renal function

Creatinine Clearance (CL_{cr}) (ml/min)	**Total TIMIRIL Daily Dose (mg/day)***		**Dose Regimen**
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	300	Two divided doses
30 – 60	75	150	Once daily or in two divided doses
15 - 30	25 - 50	75	Once daily or in two divided doses
< 15	25	25 - 50	Once daily
Supplementary dosage following haemodialysis (mg)†			
	25	50	Single dose

*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 adjustment is required for patients with hepatic impairment (see section 5.2).

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.

Paediatric population

The safety and effectiveness of **TIMIRIL** in patients below the age of 18 years has not been established.

Method of administration

TIMIRIL is given orally with or without food.

4.3 Contraindications

TIMIRIL is contraindicated in patients with hypersensitivity to pregabalin or to any of the excipients (see section 6.1).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

There have been reports in the post-marketing reports of hypersensitivity reactions in patients shortly after initiation of treatment with pregabalin as in **TIMIRIL**, including cases of angioedema and urticaria. **TIMIRIL** 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

TIMIRIL treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have 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 the medication.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with **TIMIRIL**, withdrawal symptoms have been observed in some patients. The following events have been reported: insomnia, headache, nausea and diarrhoea.

Renal failure

Cases of renal failure have been reported and in some cases discontinuation or the dose reduction of pregabalin did show reversibility of this adverse reaction.

Congestive heart failure

There have been post-marketing reports of congestive heart failure or deterioration of heart failure in some patients receiving **TIMIRIL.**

TIMIRIL should be used with caution in patients with congestive heart failure.

Diabetic patients

Diabetic patients who gain weight on **TIMIRIL** treatment may need to adjust hypoglycaemic medicinal products.

Suicidal ideation and behaviour

Patients treated with anti-epileptic medicines have reported suicidal ideation and behaviour. Studies of anti-epileptic medicines has shown a slight increased risk of suicidal ideation and behaviour.

Reduced lower gastrointestinal tract function

Reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) has been reported when pregabalin, as contained in **TIMIRIL** was given with medications such as opioid analgesics. If pregabalin and opioids are to be used in combination, measures to prevent constipation may be considered (especially in female patients and the elderly).

Misuse, abuse potential or dependence

Patients on **TIMIRIL** should be monitored for symptoms of misuse, abuse or dependence as cases of the dose escalation, drug-seeking behaviour and development of tolerance have

been reported. Caution should be used in patients with a history of substance abuse.

Encephalopathy

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

4.5 Interaction with other medicines and other forms of interaction

Since **TIMIRIL** 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, **TIMIRIL** is unlikely to produce, or be subject to, pharmacokinetic interactions.

No clinically relevant pharmacokinetic interactions were observed in studies, between **TIMIRIL** and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral anti-diabetics, diuretics insulin, phenytoin, carbamazepine, valproic acid, lamotrigine, phenobarbitone, tiagabine and topiramate, had no clinically significant effect on pregabalin clearance.

Central nervous system influencing medical products

TIMIRIL appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. **TIMIRIL** may potentiate the effects of ethanol and lorazepam. In post-marketing experience, there are reports of respiratory failure and coma in patients taking **TIMIRIL** and other central nervous system (CNS) depressant medications.

Oral contraceptives norethisterone and/or ethinyl oestradiol

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

As the potential risk of **TIMIRIL** to humans is unknown, effective contraception must be used in women of child-bearing potential.

Pregnancy

There isn't adequate data on the use of **TIMIRIL** in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown. Therefore, **TIMIRIL** should not be used during pregnancy.

Breast feeding

Pregabalin is excreted in the breast milk of humans, however, it was found to be present in the milk of rats. Therefore, breastfeeding is not recommended.

Fertility

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

4.7 Effects on ability to drive and use machines

TIMIRIL frequently causes dizziness, somnolence, blurred vision and other CNS signs and symptoms. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether TIMIRIL affects their ability to perform activities (see section 4.4).

4.8 Undesirable effects

a. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Neutropenia
Metabolism and nutrition disorders	Frequent	Increased appetite
	Less frequent	Hypoglycaemia, anorexia
Psychiatric disorders	Frequent	Euphoric mood, confusion, decreased libido, irritability
	Less frequent	Depersonalisation, anorgasmia, restlessness, depression, agitation, mood swings, insomnia, depressed mood, word finding difficulty, hallucination, abnormal dreams, increased libido, panic attack, apathy, disinhibition, elevated mood
Nervous system disorders	Frequent	Dizziness, somnolence, ataxia, disturbance in attention, abnormal coordination, memory impairment, tremor, dysarthria, paraesthesia

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Less frequent	Cognitive disorder, hypoaesthesia, visual field defect, nystagmus, speech disorder, myoclonus, hyporeflexia, dyskinesia, psychomotor hyperactivity, dizziness postural, hyperaesthesia, ageusia, burning sensation, intention tremor, stupor, syncope
	Frequency unknown	Headache, loss of consciousness, mental impairment, reversible paralysis
Eye disorders	Frequent	Vision blurred, diplopia
	Less frequent	Visual disturbance, dry eye, eye swelling, visual acuity reduced, eye pain, asthenopia, increased lacrimation, photopsia, eye irritation, mydriasis, oscillopsia, altered visual depth perception, peripheral vision loss, strabismus, visual brightness

MedDRA system organ class	**Frequency**	**Adverse reactions**
Ear and labyrinth disorders	Frequent	Vertigo
	Less frequent	Hyperacusis
Cardiac disorders	Less frequent	Tachycardia, atrioventricular block first degree, sinus tachycardia, sinus bradycardia
	Frequency unknown	Congestive heart failure
Vascular disorders	Less frequent	Flushing, hot flushes, hypotension, peripheral coldness, hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Dyspnoea, nasal dryness, nasopharyngitis, cough, nasal congestion, epistaxis, rhinitis, snoring, throat tightness
Gastrointestinal disorders	Frequent	Dry mouth, constipation, vomiting, flatulence
	Less frequent	Abdominal distension, salivary hypersecretion, gastroesophageal reflux disease, hypoaesthesia oral, ascites, dysphagia, pancreatitis

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Frequency unknown	Rare cases of swollen tongue have been reported, diarrhoea, nausea
Hepatobiliary disorders	Less frequent	Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST), jaundice, hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	Less frequent	Sweating, rash papular, cold sweat, urticaria
	Frequency unknown	Rare cases of face swelling have been reported, pruritus
Musculoskeletal and connective tissue disorders	Less frequent	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness, cervical spasm, neck pain, rhabdomyolysis
Renal and urinary disorders	Less frequent	Dysuria, urinary incontinence, oliguria, renal failure
	Frequency unknown	Urinary retention
Reproductive system and breast disorders	Frequent	Erectile dysfunction
	Less frequent	Ejaculation delayed, sexual

MedDRA system organ class	**Frequency**	**Adverse reactions**
		dysfunction, amenorrhoea, breast pain, breast discharge, dysmenorrhoea, breast hypertrophy
Immune system disorders	Frequency unknown	Angioedema, allergic reaction, hypersensitivity
General disorders and administration site conditions	Frequent	Fatigue, peripheral oedema, feeling drunk, oedema, gait abnormal
	Less frequent	Asthenia, fall, thirst, chest tightness, pain exacerbated, anasarca, pyrexia, rigors
Investigations	Frequent	Weight increase
	Less frequent	Blood creatine phosphokinase increased, platelet count decreased, blood glucose increased, blood creatinine increased, blood potassium decreased, weight decreased, white blood cell count decreased.

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

There were no unexpected adverse reactions reported in overdoses up to 15 g.

In post-marketing experiences, the following adverse events were commonly reported when **TIMIRIL** was taken in overdose: affective disorder, somnolence, confused state, agitation and restlessness.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 2.5 Central nervous system depressants -Anticonvulsants, including anti-epileptics.

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).

Mechanism of action

Pregabalin binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin has not been fully elucidated, results from animal studies suggest that binding to the alpha$_2$-delta subunit may be involved in pregabalin's anti-nociceptive effects.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. Pregabalin prevents pain-related behaviours in animal models of neuropathic and post-surgical pain, including hyperalgesia and allodynia.

5.2 Pharmacokinetic properties

Absorption

Following oral administration of pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1 hour. 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 relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Distribution

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0,56 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in animal studies. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled

pregabalin, approximately 98 % of the radioactivity recovered in the urine as unchanged pregabalin. The N-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0,9 % of the dose. In preclinical studies, Pregabalin (S-enantiomer) did not undergo racemisation to the R-enantiomer.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged medicine with a mean elimination half-life of 6,3 hours. Pregabalin elimination is nearly proportional to creatinine clearance.

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 dosage range. Inter-subject pharmacokinetic variability for pregabalin is low (< 20 %). Multiple dose pharmacokinetics are predictable from single-dose data. There is therefore no need for routine plasma concentrations monitoring of pregabalin.

Pharmacokinetics in special patient groups

Gender:

Studies have shown that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

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, dose reduction in patients with renal impairment and dosage supplementation following haemodialysis is necessary (see section

4.2).

Hepatic impairment:

There have been no specific pharmacokinetic studies conducted in patients with hepatic impairment. Pregabalin is predominantly excreted unchanged in the urine by renal elimination, and it is therefore unlikely that hepatic impairment will have significant effects on pregabalin plasma concentrations.

Elderly (over 65 years of age):

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TIMIRIL 25, 50 & 150 contains the following excipients:

Capsule content:

Pregelatinized starch

Talc

Capsule cap and body:

Gelatin

Titanium dioxide (E171)

TIMIRIL 75, & 100 contains the following excipients:

Capsule content:

Pregelatinized starch

Talc

Capsule cap and body:

Gelatin

Titanium dioxide (E171)

Red iron oxide (E172)

Printing ink for **TIMIRIL 25, 50, 75, 100 & 150** contains:

Black iron oxide (E172)

Potassium hydroxide

Propylene glycol

Shellac

Strong ammonia solution

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years. Store at or below 25 °C.

6.4 Special precautions for storage

HDPE Bottles: Keep the bottle tightly closed until use. Blisters: Do not remove blisters from carton until required for use.

6.5 Nature and contents of container

TIMIRIL 25

White HDPE bottle sealed with a white child resistant cap containing 90 capsules.

TIMIRIL 50

Clear PVC/Aluminium blisters containing 100 capsules. Blisters are enclosed in a cardboard carton.

White HDPE bottle sealed with a white child resistant cap containing 90 capsules.

TIMIRIL 75

Clear PVC/Aluminium blisters containing 100 capsules. Blisters are enclosed in a cardboard carton.

White HDPE bottle sealed with a white child resistant cap containing 90 capsules.

TIMIRIL 100

Clear PVC/Aluminium blisters containing 100 capsules. Blisters are enclosed in a cardboard carton.

White HDPE bottle sealed with a white child resistant cap containing 90 capsules.

TIMIRIL 150

Clear PVC/Aluminium blisters containing 100 capsules.

White HDPE bottle sealed with a white child resistant cap containing 90 capsules. Blisters are enclosed in a cardboard carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma SA (Pty) Ltd

106 16th Road

Building 2

Midrand, 1685

South Africa

8 REGISTRATION NUMBER(S)

Timiril 25: 54/2.5/0767

Timiril 50: 54/2.5/0768

Timiril 75: 54/2.5/0769

Timiril 100: 54/2.5/0770

Timiril 150: 54/2.5/0771

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 July 2022

10 DATE OF REVISION OF THE TEXT