

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

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

Therapeutic indications

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

Posology and method of administration

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

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:

$$CL_{cr} \text{ (ml/min)} = \frac{(140 - \text{age}) \times \text{Weight (kg)}}{0.82 \times \text{Serum creatinine } (\mu\text{mol/l})}$$

*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.

Contraindications

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

Special warnings and precautions for use

Hypersensitivity reactions
There have been reports in the post-marketing reports of hypersensitivity reactions in patients shortly after the start 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 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

In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.

Suicidal ideation and behaviour

Patients treated with anti-epileptic agents have reported suicidal ideation and behaviour. Studies of anti-epileptic drugs 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 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 at-risk patients and the elderly).

Misuse, abuse potential or dependence

There is no evidence that 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.

Interaction with other medicines and other forms of interaction

Since TIMIRIL is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans 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. Pharmacokinetic interactions were observed with oral anti-diabetics, diuretics insulin, phenytoin, carbamazepine, valproic acid, lamotrigine, phenobarbital, 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 contraceptive 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.

Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

As there is no evidence that 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.

Effects on ability to drive and use machines

Patients treated with anti-epileptic agents, blurred vision, 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).

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
Psychiatric disorders	Less frequent	Hypoglycaemia, anorexia
Nervous system disorders	Frequent	Euphoric mood, confusion, decreased libido, irritability
Eye disorders	Less frequent	Depersonalisation, anorgasmia, restlessness, depression, agitation, mood swings, insomnia, depressed mood, word finding difficulty, hallucination, abnormal dreams, increased libido, panic attack, apathy, disimhibition, elevated mood
Respiratory, thoracic and mediastinal disorders	Less frequent	Dizziness, somnolence, ataxia, disturbance in attention, abnormal coordination, memory impairment, tremor, dysarthria, paraesthesia
Cardiac disorders	Less frequent	Cognitive, speech disorder, myoclonus, hyporeflexia, dyskinesia, psychomotor hyperactivity, dizziness postural, hyperaesthesia, ageusia, burning sensation, intention tremor, stupor, syncope
Vascular disorders	Less frequent	Headache, loss of consciousness, mental impairment, reversible paralysis
Respiratory, thoracic and mediastinal disorders	Less frequent	Headache, loss of consciousness, mental impairment, reversible paralysis
Cardiac disorders	Less frequent	Headache, loss of consciousness, mental impairment, reversible paralysis
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