

**MODULE I : ADMINISTRATIVE PARTICULARS OF THE PRODUCT****1.3 Product Information****1.3 Product Information****1.3.1 Summary of Product Characteristics (SmPC)****1. Name of the medicinal product****1.1 (Invented) Name of the medicinal product**

**SYRENEV PLUS (PREGABALIN AND METHYLCOBALAMIN CAPSULES (75MG/750MCG))**

**1.2 Strength**

Each hard gelatin capsule contains:

Pregabalin BP 75 mg

Methylcobalamin 750 mcg

Excipients Q.S.

Approved colour used in empty capsule shell.

**1.3 Pharmaceutical Form**

Hard Gelatin Capsule

**2. Qualitative and Quantitative Formula**

**Batch Size:** 1,00,000 Capsules

Sr. No.	Name of Ingredient	Quantity/ Capsule (mg)	Quantity/ Batch (Kg)	%	Functions
<b>Mixing</b>					
1.	Pregabalin BP	75.000	7.500	30.000%	Anti-epileptics
2.	Colloidal anhydrous silica BP	2.000	0.200	0.800%	Disintegrant
3.	Base Granules of Starch/DCP IHS	165.060	16.506	66.024%	Diluent
4.	Croscarmellose sodium BP	5.000	0.500	2.000%	Disintegrant
5.	Magnesium Stearate BP	2.000	0.200	0.800%	Lubricant
6.	Methylcobalamin IHS	0.940	0.094	0.376%	Anti-anemic agent
<b>Total Weight of Filled Powder</b>		<b>250.000 mg</b>	<b>25.000 Kg</b>	<b>100%</b>	
7.	Capsule Maroon/yellow size "2" IHS	Q.S.	1,00,000 Nos.	---	Capsule Shell

**3. Pharmaceutical form**

Maroon/Yellow colored hard gelatin capsule containing with white colored powder ("2" size) capsule.

**1.3 Product Information****4. Clinical particulars:****4.1 Therapeutic Indication:**

Pregabalin / Methylcobalamin are used for the treatment, control, prevention, & improvement of the following diseases, conditions and symptoms:

- Nerve damage pain
- Pain in neurological disorders
- Nerve damage
- Seizures
- Anxiety disorder in adults
- Anemia
- Numbness and tingling

**4.2 Posology and method of administration:**

The dose range is 150 to 600 mg per day given in either two or three divided doses along with Methylcobalamin 1.5 mcg to 6.0 mg. Pregabalin treatments Can be started at a dose of 150 mg per day given as two or three divided doses & methylcobalamin 1.5 mg per day. The dose may be increased to 300 mg per days after an interval of 3 of 7 days, and if needed, to a maximum dose of 600 mg per day.

**4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

**4.4 Special warnings and precautions for use:**Diabetic patients

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

Hypersensitivity reactions

There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin 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 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 the medicinal product.

Vision-related effects

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients.

In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

Renal failure

**1.3 Product Information**

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

Withdrawal of concomitant antiepileptic medicinal products

There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness. 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 use or shortly after discontinuing pregabalin.

Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dose of pregabalin.

Congestive heart failure

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

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 medicinal products (e.g. anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for pregabalin.

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 medications that have the potential to produce constipation, such as opioid analgesics. When pregabalin and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).

Abuse potential

Cases of abuse 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 abuse.

**1.3 Product Information**Encephalopathy

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

Lactose intolerance

Lyrica contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

**4.5 Interaction with other medicinal products 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 drug metabolism in vitro, and is not bound to plasma proteins, it 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 and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Oral contraceptives, norethisterone and/or ethinyl oestradiol

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

CNS influencing medical products

Pregabalin may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

Interactions and the elderly

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

**4.6 Adverse Drug Reactions**

- Drowsiness,
- dizziness,
- dry mouth,
- constipation,
- difficulty concentrating, or weight gain

**4.7 Fertility, Pregnancy and lactation**

Women of childbearing potential / Contraception in males and females

As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

**Pregnancy**

There are no adequate data from the use of pregabalin in pregnant women.

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

**1.3 Product Information**

Lyrica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

**Breast-feeding**

It is not known if pregabalin is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breast-feeding is not recommended during treatment with pregabalin.

**Fertility**

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

In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.

A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown.

**4.8 Effects on ability to drive and use machines:**

When driving vehicles or operating machines it should be taken into account that occasionally dizziness, tiredness or confusion may occur.

**4.9 Overdose:**

In overdoses up to 15 g, no unexpected adverse reactions were reported.

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.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

**5. Pharmacological properties****5.1 Pharmacotherapeutic Group**

**Pharmacotherapeutic group:** Antiepileptics, other antiepileptics

**ATC code:** N03AX16

**5.2 Pharmacodynamic properties**Mechanism of action

Pregabalin binds to an auxiliary subunit ( $\alpha_2$ - $\delta$  protein) of voltage-gated calcium channels in the central nervous system,

Clinical Efficacy and safety**Neuropathic pain**

Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33% of

**1.3 Product Information**

patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo. In the controlled clinical trial in central neuropathic pain 22% of the Pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.

**Epilepsy****Adjunctive Treatment**

Pregabalin has been studied in 3 controlled clinical trials of 12 week duration with either twice a day dosing (BID) or three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

A reduction in seizure frequency was observed by Week 1.

**Monotherapy (newly diagnosed patients)**

Pregabalin has been studied in 1 controlled clinical trial of 56 week duration with twice a day dosing (BID). Pregabalin did not achieve non-inferiority to lamotrigine based on the 6-month seizure freedom endpoint. Pregabalin and lamotrigine were similarly safe and well tolerated.

**Generalised Anxiety Disorder**

Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 months duration.

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.

In controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated fundoscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with pregabalin, and 4.8% of placebo-treated patients. Visual field changes were detected in 12.4% of pregabalin-treated, and 11.7% of placebo-treated patients. Fundoscopic changes were observed in 1.7% of pregabalin-treated and 2.1% of placebo-treated patients.

**5.3 Pharmacokinetic properties**

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

**Absorption**

Pregabalin is rapidly 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  $\geq 90\%$  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 preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present

**1.3 Product Information**

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.

**Biotransformation**

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled 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 preclinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

**Elimination**

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

Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance.

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.

**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, there is no need for routine monitoring of plasma concentrations of pregabalin.

**Gender**

Clinical trials indicate 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 dose supplementation following haemodialysis is necessary.

**Hepatic impairment**

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug 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 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.

**5.4 Preclinical safety data**

In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long term exposure to pregabalin at exposures  $\geq$  5 times the mean human exposure at the maximum recommended clinical dose.

## MODULE I : ADMINISTRATIVE PARTICULARS OF THE PRODUCT



### 1.3 Product Information

Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.

Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.

Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests.

Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long term clinical data. There is no evidence to suggest an associated risk to humans.

In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

## 6. Pharmaceutical particulars

### 6.1 List of Excipients

Excipients	Specification
Colloidal anhydrous silica	BP
Base Granules of Starch/DCP	IHS
Croscarmellose sodium	BP
Magnesium Stearate	BP

### 6.2 Incompatibilities

Not Applicable

### 6.3 Shelf life

24 months from the date of manufacturing.

### 6.4 Special precautions for storage

Store in a dry place below 30°C, protected from light & moisture.

### 6.5 Nature and contents of container

3 x 10 Capsules Alu-Alu Blisters packed in printed carton along with package insert.



<b>MODULE I : ADMINISTRATIVE PARTICULARS OF THE PRODUCT</b>	 Sunrise Remedies Pvt. Ltd. Ethical Healthcare. Affordable.
<b>1.3 Product Information</b>	

**6.6 Special precautions for disposal**

No special requirements.

**7. REGISTRANT**

**SUNRISE REMEDIES PVT. LTD.**

At: Block No. 2244, At & Post- Santej,  
Tal- Kalol. Dist- Gandhinagar.

**8. DATE OF REVISION OF THE TEXT**

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**9. NAME AND ADDRESS OF MANUFACTURER**

**SUNRISE REMEDIES PVT. LTD.**

At: Block No. 2244, At & Post- Santej,  
Tal- Kalol. Dist- Gandhinagar.