SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) FOR DRUG PRODUCTS IN NIGERIA

1. **NAME OF THE DRUG PRODUCT**
   Brand Name: SUBLIME-75
   Generic Name: Prgabalin capsule 75 mg

   Strength: 75 mg

   Dosage form: Hard gelatin capsule

   Rout of administration: Oral

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Label claim:
   Each Hard gelatin capsule contains:
   Prgabalin BP 75 mg
   Excipients Q.S.
   Approved colour used in Empty hard gelatin shell

   UNIT FORMULA:

Sr. No.	Ingredient	Reference	Label Claim (mg)	Overages (%) **	Qty. per cap (mg)	Function
1.	Pregabalin	BP	75.00	--	75.00	Active
2.	Lactose	BP	--	--	100.00	Diluent
3.	Starch (SP-Maize starch powder)	BP	--	--	65.00	Diluent
4.	Sodium lauryl sulphate	BP	--	--	5.00	Disintegrant
5.	Calcium Silicate	USP	--	--	5.00	Anticaking Agent
6.	Magnesium Stearate	BP	--	--	5.00	Lubricant
7.	Empty hard gelatin capsule size “2” plain Colour: Red/White	IH	1.0 Nos	3 %	1.030	Capsule shell
Total weight				--	255.0 mg	--

3. **PHARMACEUTICAL FORM**
   Hard Gelatin Capsule

   Red/White coloured hard gelatin capsule size "2" which containing white colour powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

Neuropathic pain

It is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy

It is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised Anxiety Disorder

It is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

4.2 Posology/Dosage and method of administration:

Posology

The dose range is 150 to 600 mg per day given in either two or three divided doses.

Neuropathic pain

Pregabalin treatment can be started at a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.

Epilepsy

Pregabalin treatment can be started with a dose of 150 mg per day given as two or three divided doses. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. The maximum dose of 600 mg per day may be achieved after an additional week.

Generalised Anxiety Disorder

The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.

Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. Following an additional week the dose may be increased to 450 mg per day. The maximum dose of 600 mg per day may be achieved after an additional week.

Renal impairment: Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As pregabalin clearance is directly proportional to creatinine clearance.

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

Creatinine clearance (CLcr) (mL/min)	**Total pregabalin daily dose***		**Dose regimen**
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	600	BID or TID
≥ 30 - <60	75	300	BID or TID
≥ 15 - <30	25-50	150	Once Daily or BID
< 15	25	75	Once Daily
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose+

TID = Three divided doses
BID = Two divided doses
* Total daily dose (mg/day) should be divided as indicated by dose regimen provide mg/dose + Supplementary dose is a single additional dose

Paediatric population: The safety and efficacy of Pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been established.
Elderly: Elderly patients may require a dose reduction of pregabalin due to a decreased renal function.

Method of administration: Oral

4.3 Contraindication:
Hypersensitivity to the active substance or to any of the excipients listed in. section 6.1

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 post marketing 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.

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression.

Pregabalin use in the first-trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment.

Renal failure
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.
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.

4.5 Interaction with other drug 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.
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.

Pregabalin may potentiate the effects of ethanol and lorazepam.
In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other central nervous system (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 Fertility, pregnancy and lactation
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.

Pregabalin Capsules 75Mg should not be used during pregnancy unless clearly necessary

Breast-feeding

Pregabalin is excreted into human milk. The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

Pregabalin Capsules 75 Mg may have minor or moderate influence on the ability to drive and use machines. Pregabalin Capsules 75 Mg may cause dizziness and somnolence and therefore may influence the ability to Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

The adverse reactions listed may also be associated with the underlying disease and/or concomitant medicinal products.

Pregabalin adverse drug reactions System Organ Class	**Adverse drug reactions**
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropaenia
Immune system disorders	
Uncommon	*Hypersensitivity*
Rare	*Angioedema, allergic reaction*
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, libido decreased, disorientation, insomnia
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition,
Nervous system disorders	
Very Common	Dizziness, somnolence, headache
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy

Uncommon	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*
Rare	*Convulsions*, hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, Visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation,
Rare	*Vision loss, keratitis,* oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, *Congestive heart failure*
Rare	QT prolongation, sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Flushing, hot flushes, hypotension, hypertension, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	*Pulmonary oedema,* throat tightness
Not known	Respiratory depression
Gastrointestinal disorders	
Common	*Vomiting*, *nausea,* dry mouth, constipation, *diarrhoea,* flatulence, abdominal distension
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, dysphagia, *Swollen tongue*

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics and antipyretics, ATC code: N02BF02

Mechanism of action:

The active substance, pregabalin, is a gamma-aminobutyric acid 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.

5.2 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 ≥ 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 Cmax by approximately 25-30 % and a delay in tmax 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 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

5.3 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 ≥ 5 times the mean human exposure at the maximum recommended clinical dose.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Sr. No	Excipients	Pharmacopeia
1	Lactose	BP
2	Starch (SP- Maize starch powder)	BP
3	Sodium lauryl sulphate	BP
4	Calcium Silicate	USP
5	Magnesium Stearate	BP
6	Empty hard gelatin capsule size "2" plain Colour: Red/White	IHS

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store below 30^{O} C in dry & dark place.

6.5 Nature and contents of container

An alu-pvc blister containing 10 capsules such 10 blisters are packed in carton along with pack insert.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements for disposal.

7. APPLICANT/HOLDER OF CERTIFICATE OF PRODUCT REGISTRATION
M/S. SUBLIME STAR PHARMACEUTICAL LIMITED.
Olivia Mall, Plot 334,
Rafiu baba Tunde Tinubu,
Amuwo Odofin,
Lagos State, Nigeria.

8. DRUG PRODUCT MANUFACTURER
SWISS PHARMA PVT. LTD. 3709,
G.I.D.C. Phase IV, Vatva,
Ahmedabad –382445, India
www.swisspharma.in

9. NAFDAC REGISTRATION NUMBER(S): New Registration