SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

Product Name: Pregabalin Capsules **7**5 mg

1.2 Strength: 75 mg

1.3 Pharmaceutical Dosage Form: Solid Dosage form (Capsule)

2. QUALITATIVE AND QUANTITATIVES COMPOSITION:

Composition:

Each hard Gelatin capsule contains:

Pregabalin BP 75mg

Excipients q.s

Batch Size- 200000 Capsules

Sr.no	**Composition**
1	Pregabalin
2	Lactose
3	Colloidal silicon dioxide (Aerosil 200)
4	Talcum powder
5	EHG Capsules size '2' Green /White

3. PHARMACEUTICAL FORM:

Visual description of finished product:

Green/White coloured size "2" empty hard gelatin Capsules filled with white to off-white colour powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications and Usage

Neuropathic pain

Pregabalin is indicated for the treatment of neuropathic pain in adults.

Epilepsy

Pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization.

Generalized Anxiety Disorder

Pregabalin is indicated for the treatment of Generalized Anxiety Disorder (GAD) in adults.

4.2. Posology 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.

Discontinuation of pregabalin

In accordance with current clinical practice, if pregabalin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication

Special populations

Patients with 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, dose reduction in patients with compromised renal

function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

$$CL_{cr}(ml/min) = \left[\frac{1.23 \times [140 - age\,(years)] \times weight\,(kg)}{serum\ creatinine\ (\mu mol/l)} \right] (\times\ 0.85 \text{ for female patients})$$

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

Table 1. Pregabalin dose adjustment based on renal function

Creatinine clearance (CL_{cr}) (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 to provide mg/dose

[+] Supplementary dose is a single additional dose

Use in patients with hepatic impairment

No dose adjustment is required for patients with hepatic impairment.

Paediatric population

Use in children and adolescents (12-17 years of age)

The safety and efficacy of Pregabalin Capsule in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. No data are available.

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of Pregabalin due to a decreased renal function (see patients with renal impairment).

Method of administration

Pregabalin may be taken with or without food.

Pregabalin is for oral use only.

4.3. Contraindications

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

4.4. Special Warning and Precautions for use

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medications.

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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.

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 and diarrhoea.

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Because there are limited data on severe congestive heart failure patients, pregabalin should be used with caution in these patients.

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.

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.

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

Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam.

4.6. Pregnancy and lactation

Pregnancy

There are no adequate data on the use of Pregabalin in pregnant women.

Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown. Therefore, Pregabalin should not be used during pregnancy unless the benefit to the mother clearly

outweighs the potential risk to the foetus. Effective contraception must be used in women of child bearing potential.

Lactation

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.

4.7 Effects on ability to drive and use machines

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

4.8. Undesirable Effects

The most commonly reported adverse reactions were dizziness and somnolence.

Adverse reactions were usually mild to moderate in intensity.

In all controlled studies, the discontinuation rate due to adverse reactions was 13% for patients receiving Pregabalin and 7% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from Pregabalin treatment groups were dizziness and somnolence.

Immune system disorder: Allergic reaction, hypersensitivity

Nervous system disorders: Headache

Cardiac disorders: Congestive heart failure

Gastrointestinal disorders: Swollen tongue, diarrhea, nausea

Skin and subcutaneous tissue disorders: Face swelling, pruritus

4.9. Overdose and special antidotes

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

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamics properties:

Mechanism of Action

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's antinociceptive and antiseizure effects in animal models. In vitro, pregabalin reduces the calcium-dependent release of several neurotransmitters, possibly by modulation of calcium channel function.

While pregabalin is a structural derivative of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), it does not bind directly to GABAA, GABAB, or benzodiazepine receptors, does not augment GABAA responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake

5.2 Pharmacokinetics Properties

Preclinical Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption

Following oral administration of Pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is ≥ 90% and is independent of dose. Following single- (25 to 300 mg) and multiple-dose (75 to 900 mg/day) administration, maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of Pregabalin absorption is decreased when given with food, resulting in a decrease in Cmax of approximately 25% to 30% and an increase in Tmax to approximately 3 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 0.5 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 mice, rats, and monkeys. 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 radiolabeled Pregabalin, approximately 90% of the administered dose was 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 racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 ml/min in young healthy subjects. Because Pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr).

5.3 Preclinical safety data:

-There is no preclinical safety data

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EXCIPIENTS	SPECIFICATION
Lactose	BP
Colloidal Anhydrous silica (Aerosil 200)	BP
Talcum powder	BP
EHG Capsules size ‘2’ Green /White	In-House

6.2 Incompatibilities: Not Applicable.

6.3 Shelf life: 2 years (24 Months).

6.4 Special precautions for storage

Store in cool, dry & dark Place below 30^0c.

Keep out of reach of children

6.5 Nature and contents of container

Primary Packing:

10/12 capsules packed in Alu -PVDC blister

Secondary Packing:

3 x10 or 2x12 blisters are packed in a Printed Carton with a pack insert

6.6 Special precautions for disposal and other handling:

-None

7.MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

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Address: 415, Shah Nahar Ind. Estate,

Dr. E. Moses Road, Worli,

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8. MARKETING AUTHORISATION NUMBER

06976/08204/REN/2021

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Dec 28, 2021

10. DATE OF REVISION OF THE TEXT

-Not applicable.