Summary of Product Characteristics

1. Name of the Medicinal Product

Product Name: Cabalin -25 (Pregabalin Capsules 25 mg)

1.2 Strength: 25 mg

1.3 Pharmaceutical Dosage Form: Solid Dosage form (Capsule)

2. QUALITATIVE AND QUANTITATIVES COMPOSITION:

Composition:

Each hard Gelatin capsule contains:

Pregabalin 25mg

Excipients q.s

Batch Size- 200000 Capsules

Sr.no.	Composition	Specification	Label claim (mg)	Quantity/ Capsule(mg)	Quantity / batch (kg)	Function
1	Pregabalin	In-House	25	25	5.00	API
2	Lactose	BP 2013	-	257.2	51.440	Diluent
3	Colloidal silicon dioxide (Aerosil 200)	BP 2013	-	1.3	0.260	Glidants
4	Talcum powder	BP 2013	-	1.5	0.300	Lubricant
5	EHG Capsules size '2' Blue /White	In-House	-	1 No	204000.00 NoS	Carrier

3. PHARMACEUTICAL FORM:

Visual description of finished product:

Blue/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.

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Generalized Anxiety Disorder

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

4.2. Dosage and 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

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Dosage reduction in patients with compromised renal function must be individualized according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

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

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 (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 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

Use in patients with hepatic impairment

No dosage adjustments is required for patients with hepatic impairment.

Pediatric 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.

The use in children is not recommended.

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.

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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.

47. 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 Pharmacodynamic properties:

Pharmacotherapeutic group: Antiepileptics, ATC code: N03AX16

Mechanism of Action

Pregabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin.

5.2 Pharmacokinetics Properties

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

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 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 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.

Metabolism

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.

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.

5.3 Preclinical safety data:

-There is no preclinical safety data

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6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

EXCIPIENTS	SPECIFICATION
Lactose	BP
Colloidal Anhydrous silica (Aerosil 200)	BP
Talcum powder	BP

6.2 Incompatibilities: Not Applicable.

6.3 Shelf life: 2 years (24 Months)

6.4 Special precautions for storage

Store in dry Place below 30^0 C. Protect from Light.

Keep out of reach of children

6.5 Nature and contents of container

Primary Packing

12 capsules are packed in Alu -PVDC blister.

Secondary Packing:

2 packs of 12 capsules 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

Cachet Pharmaceuticals Private Limited

Telephone: +91-22-24970011 / +91-22-40829999

8. MARKETING AUTHORISATION NUMBER

-Not Applicable

Summary of Product Characteristics

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

-Not applicable

10. DATE OF REVISION OF THE TEXT

-Not applicable

11. NAME AND ADDRESS OF MANUFACTURE

Cachet Pharmaceuticals Private Limited

Address: Village: Thana, Baddi, Himachal Pradesh-173 205, India