Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

PROBION 75

2. Qualitative and quantitative composition

Each hard gelatin capsule contains pregabalin BP 75 mg.
Excipient with known effect: each capsule contains 207.2 mg of lactose.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Hard Gelatin capsule.
Green and white coloured size "2" hard gelatin capsules filled with a white to off-white powder.

4. Clinical particulars

4.1 Therapeutic indications

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 generalisation.

Generalised anxiety disorder

Pregabalin is indicated for the treatment of generalised anxiety disorder 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: 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: 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 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. Treatment can be started at 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, to 450 mg per day after a further week, and to the maximum dose of 600 mg per day after an additional week.

Discontinuation of pregabalin
In accordance with current clinical practice, if pregabalin has to be discontinued it is recommended that this be done gradually over a minimum of 1 week, independent of the indication.
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 as indicated in Table 1.
Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, the 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 to < 60	75	300	BID or TID
≥ 15 to < 30	25–50	150	Once daily or BID
< 15	25	75	Once daily
Supplementary dose following haemodialysis (mg)	25	100	Single dose[+]

BID = two divided doses; TID = three divided doses. *Total daily dose should be divided as indicated by the dose regimen to provide the dose per administration. [+]Supplementary dose is a single additional dose.

Patients with hepatic impairment
No dose adjustment is required for patients with hepatic impairment.
Paediatric population
The safety and efficacy of pregabalin capsules in children below the age of 12 years and in adolescents (12–17 years of age) have not been established. No data are available.
Elderly (over 65 years of age)
Elderly patients may require a dose reduction due to decreased renal function (see patients with renal impairment above).
Method of administration
For oral use only. Pregabalin may be taken with or without food.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings and precautions for use
Excipients
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Diabetic patients

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

Dizziness, somnolence and accidental injury

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

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 reported: insomnia, headache, nausea and diarrhoea.

Congestive heart failure

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 oedema and cardiovascular complications such as hypertension or congestive heart failure. Because there are limited data in patients with severe congestive heart failure, 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 (less than 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 ethinylestradiol 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 and the potential risk to humans is unknown. Pregabalin should therefore 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 childbearing potential.

Breast-feeding

It is not known whether pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Breast-feeding is therefore not recommended during treatment with pregabalin.

4.7 Effects on ability to drive and use machines

Pregabalin may cause dizziness and somnolence and may therefore 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 medicinal product 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.

Reactions listed in the submitted document

Immune system disorders: allergic reaction, hypersensitivity.
Nervous system disorders: headache.
Cardiac disorders: congestive heart failure.
Gastrointestinal disorders: swollen tongue, diarrhoea, nausea.
Skin and subcutaneous tissue disorders: face swelling, pruritus.

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose

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

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, and 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 Pharmacokinetic properties

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 under fasting conditions, peak plasma concentrations occur within 1.5 hours. Oral bioavailability is ≥ 90% and is independent of dose. Following single (25 to 300 mg) and multiple-dose (75 to 900 mg/day) administration, Cmax and 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 absorption is decreased when pregabalin is 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 with food has no clinically relevant effect on total absorption, so pregabalin can be taken with or without food.

Distribution

Pregabalin does not bind to plasma proteins. The apparent volume of distribution following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for the 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, to cross the placenta in rats, and to be present in the milk of lactating rats.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 90% of the administered dose was recovered in the urine as unchanged pregabalin. The N-methylated derivative, the major metabolite found in urine, accounted for 0.9% of the dose. In preclinical studies, pregabalin (the S-enantiomer) did not undergo racemisation 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.

5.3 Preclinical safety data

There is no preclinical safety data

6. Pharmaceutical Particulars

6.1 List of Excipients

Capsule contents

Lactose
Colloidal anhydrous silica
Talcum powder
EHG Capsules size 2 Green/White

6.2 Incompatibilities

Not applicable.

6.3 Shelf-Life

2 years (24 months).

6.4 Special Precautions for storage

Store in a cool, dry, dark place below 30°C. Keep out of the reach of children.

6.5 Nature and Content of container

12 capsules packed in an Alu-PVDC blister. Two blisters of 12 capsules are packed in a printed carton together with a pack insert.

6.6 Special precautions for disposal and other handling

None

7. Marketing Authorization Holder

Cachet Pharmaceuticals Private Limited
415, Shah Nahar Industrial Estate, Dr. E. Moses Road, Worli, Mumbai – 400 018, Maharashtra, India.
Telephone: +91-22-24970011 / +91-22-40829999

8. Marketing Authorization Number
H2022/CTD9252/19821

9. Date of first authorization/renewal of the authorization
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10. Date of revision of the text
2023 May 03