SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
PREGAVALEX (PREGABALIN)75 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 75 mg Pregabalin
Excipient with known effect

Each capsule contains 59mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard gelatin capsule

4. Clinical Particulars:
4.1 Therapeutic indications
Neuropathic pain:
PREGAVALEX is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy:
PREGAVALEX is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization.

***Generalised Anxiety Disorder*:**
PREGAVALEX is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

Fibromyalgia:
PREGAVALEX is indicated for the management of Fibromyalgia

4.2 Method of administration:
PREGAVALEX may be taken with or without food.
PREGAVALEX for oral use only.
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.

Fibromyalgia:
The recommended dose of Pregabalin for fibromyalgia is 300 to 450 mg/day. Begin dosing at 75 mg two times a day (150 mg/day). The dose may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). Although Pregabalin was also studied at 600 mg/day, there is no evidence that this dose confers additional benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended. Because Pregabalin is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

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:

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

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 (see Table 1).

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 dose 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 :
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. 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).

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

4.4 Special warnings and special precautions for use
-*Suicidal ideation and behavior*: Suicidal ideation and behavior have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomized placebo controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behavior. 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 behaviors and appropriate treatment should be considered.

-*Diabetic patients:* In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic 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:* 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.
- *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.
In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, pregabalin (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4 % of pregabalin -treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.
-*Dependence:* In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea, consistent with physical dependence. In the post marketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.
- Encephalopathy: Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.
- Lactose intolerance: **PREGAVALEX** 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.
- Patients treated with Pregabalin for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

4.5 Interactions 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.

*Ethanol, lorazepam, oxycodone***:**
Pregabalin may potentiate the effects of ethanol and lorazepam, 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.

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

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

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. there were no effects on sperm motility.

4.7 Effects on ability to drive and use machines
Pregabalin may have minor or moderate influence on the 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 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.
All adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed below by class and frequency (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions listed may also be associated with the underlying disease and / or concomitant medicinal products.
In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased.

Adverse drug reactions:
Infections and infestations: Uncommon: Nasopharyngitis. Blood and lymphatic system disorders: Rare: Neutropenia. Immune system disorders: Frequency not known: Hypersensitivity, 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, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy, Rare: Disinhibition, elevated mood, Frequency not known: Aggression
Nervous system disorders: Very Common: Dizziness, somnolence, Common: Ataxia, coordination abnormal, tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia, sedation, balance disorder, lethargy, Uncommon: Syncope, stupor, myoclonus, psychomotor hyperactivity, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, speech disorder, hyporeflexia, hypoaesthesia, amnesia, hyperaesthesia, burning sensation, Rare: Hypokinesia, parosmia, dysgraphia, Frequency not known: Loss of consciousness, mental impairment, convulsions, headache, malaise
Eye disorders: Common: Vision blurred, diplopia, Uncommon: Visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased, Rare: Peripheral vision loss, oscillopsia, altered visual depth perception, photopsia, eye irritation, mydriasis, strabismus, visual brightness, Frequency not known: Vision loss , keratitis. Ear and labyrinth disorders: Common: Vertigo, Uncommon: Hyperacusis. Cardiac disorders: Uncommon: Tachycardia, atrioventricular block first degree, Rare: Sinus tachycardia, sinus bradycardia, sinus arrhythmia, Frequency not known: Congestive heart failure, QT prolongation. Vascular disorders: Uncommon: Flushing, hot flushes, hypotension, hypertension, Rare: Peripheral coldness Respiratory, thoracic and mediastinal disorders: Uncommon: Dyspnoea, nasal dryness, Rare: Epistaxis, throat tightness, cough, nasal congestion, rhinitis, snoring, Frequency not known: Pulmonary oedema. Gastrointestinal disorders: Common: Vomiting, dry mouth, constipation, flatulence, Uncommon: Abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral, Rare: Ascites, pancreatitis, dysphagia, Frequency not known: Swollen tongue, diarrhoea, nausea. Skin and subcutaneous tissue disorders: Uncommon: Rash papular, hyperhidrosis, Rare: Urticaria, cold sweat, Frequency not known: Stevens Johnson syndrome, pruritus. Musculoskeletal and connective tissue disorders: Uncommon: Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness, Rare: Rhabdomyolysis, cervical spasm, neck pain. Renal and urinary disorders: Uncommon: Urinary incontinence, dysuria, Rare: Renal failure, oliguria, Frequency not known: Urinary retention. Reproductive system and breast disorders, Common: Erectile dysfunction, Uncommon: Ejaculation delayed, sexual dysfunction, Rare: Amenorrhoea, breast discharge, breast pain, dysmenorrhoea, hypertrophy

breast.General disorders and administration site conditions: Common: Gait abnormal, feeling drunk, fatigue, oedema peripheral, oedema, Uncommon: Fall, chest tightness, asthenia, thirst, pain, feeling abnormal, chills, Rare: Generalised oedema, pyrexia, Frequency not known: Face oedema. Investigations: Common: Weight increased, Uncommon: Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased, Rare: Blood glucose increased, blood potassium decreased, white blood cell count decreased, blood creatinine increased, weight decreased.

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain**,** hyperhidrosis and dizziness. The patient should be informed about this at the start of the treatment.
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.

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.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:
Pharmacodynamic properties:
Pharmacotherapeutic group: Antiepileptics,ATC Code: N02BF Gabapentinoids.
The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid).

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 [^{3}H]-gabapentin.

Clinical experience:
Neuropathic pain:
Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar. In clinical trials for both peripheral and central neuropathic pain a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

Epilepsy:
The safety and efficacy profiles for BID and TID dosing regimens were similar.
A reduction in seizure frequency was observed by Week 1.

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

Management of Fibromyalgia:
The studies showed a reduction in pain by visual analog scale. In addition, improvement was demonstrated based on a patient global assessment (PGIC), and on the Fibromyalgia Impact Questionnaire (FIQ).

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 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.

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

Pharmacokinetics in special patient groups:
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate
Maize starch
Purified talc
Gelatin
Titanium dioxide
Carmoisine
Quinoline yellow(D & C no.10)
Ponceau 4R 25%

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 Years

6.4 Special precautions for storage
Keep at a temperature not exceeding 30 °C. Keep out of reach of children.

6.5 Nature and contents of container
Carton box containing 1, 2 or 3 transparent (AL/PVDC) blisters each of 10 hard gelatin capsules with insert leaflet.

6.6 Instructions for use and handling and disposal
Keep at a temperature not exceeding 30 °C. Keep out of reach of children.

7. MARKET AUTHORIZATION HOLDER
EVAPHARMA for Pharmaceutical industries

8. MARKETING AUTHORISATION NUMBER(S)

05690/07785/REN/2021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22-02-2021

10. DATE OF REVISION OF THE TEXT

24-October-2023

11. Reference