Summary of Product Characteristics (SPC)

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8. MARKETING AUTHORISATION NUMBER(S)
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10. DATE OF REVISION OF THE TEXT
1. NAME OF THE MEDICINAL PRODUCT
Nervax 75 mg Capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 75 mg of Pregabalin.
For a full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM
Hard capsules.
Brown opaque colored cap and white opaque body size “2” hard gelatin capsules imprinted with “PK75” on the body containing white to off-white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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

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

4.2 Posology and method of administration
The dose range is 150 to 600 mg per day given in either two or three divided doses.
Nervax may be taken with or without food.

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 (see section 4.8).

**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 (see section 5.2), 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:

\[
CL_{cr} (\text{ml/min}) = \frac{1.23 \times [140 \cdot \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine (\mumol/l)}} \times 0.85 \text{ for female patients}
\]

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>
<thead>
<tr>
<th>Creatinine clearance (CLcr) (ml/min)</th>
<th>Total pregabalin daily dose *</th>
<th>Dose regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Starting dose (mg/day)</td>
<td>Maximum dose (mg/day)</td>
</tr>
<tr>
<td>≥60</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td>≥30 - &lt;60</td>
<td>75</td>
<td>300</td>
</tr>
<tr>
<td>≥15 - &lt;30</td>
<td>25 – 50</td>
<td>150</td>
</tr>
<tr>
<td>&lt;15</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>Supplementary dosage following haemodialysis (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

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 (see section 5.2).

Use in children and adolescents:
Nervax is not recommended for use in children below the age of 12 years and adolescents (12 - 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).

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
Nervax is contraindicated for patients with known hypersensitivity to any of its components.

4.4 Special warnings 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.
In accordance with current clinical practice, 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.

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.
Accordingly, 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.
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 controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.
No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.
4.6 Pregnancy and lactation

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, Nervax 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.

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

Nervax 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.

Consult your Pharmacist or Physician if any side effect is observed.

4.9 Overdose

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

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics.

ATC code: N03AX16

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 (α2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin.
Clinical experience:
Neuropathic pain
Efficacy has been shown in studies in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.
Pregabalin has been studied in 10 controlled clinical studies of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.
In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.
In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33% of patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo.
In the controlled clinical trial in central neuropathic pain 22% of the Pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.
Epilepsy
Pregabalin has been studied in 3 controlled clinical studies of 12 week duration with either twice a day dosing (BID) or three times a day (TID) dosing. Overall, 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
Pregabalin has been studied in 6 controlled studies of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 months duration.
Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.
In controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.
In controlled studies, 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. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated funduscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with pregabalin, and 4.8% of placebo-treated patients. Visual field changes were detected in 12.4% of pregabalin-treated, and 11.7% of placebo-treated patients. Funduscopic changes were observed in 1.7% of pregabalin-treated and 2.1% of placebo-treated patients.

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 $C_{\text{max}}$ by approximately 25-30% and a delay in $t_{\text{max}}$ 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 (see section 5.2 Renal impairment).

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see Section 4.2 Table 1).

**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 (see section 4.2 Table 1).
- **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 (see section 4.2 Table 1).
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.

Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests. Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short-term and limited long-term clinical data. There is no evidence to suggest an associated risk to humans.

In juvenile rats, the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats 1-2 weeks after exposure at > 2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
- Mannitol Granular
- Sodium Starch Glycolate
- Talc
- Colloidal Silicon Dioxide

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years.

Nervax 75 mg Capsules
6.4 Special precautions for storage
Keep at room temperature (15-30°C).
Do not use beyond the expiry date or if the product shows any sign of deterioration.

6.5 Nature and contents of container
Two Aluminum-PVC/PVDC blisters of 10 capsules each, packed in a printed carton with folded leaflet.

6.6 Special precautions for disposal and other handling
No special requirements.

7. MARKETING AUTHORISATION HOLDER
Tabuk Pharmaceutical Manufacturing company.
Almalaz Area.
Salah Adeen Street.
11437
Riyadh
Kingdom of Saudi Arabia

8. MARKETING AUTHORIZATON NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

10. DATE OF REVISION OF THE TEXT