Pregaforte®

Pregabalin

FORMS AND PRESENTATION
Pregaforte®25: Capsules: Box of 30.
Pregaforte®75: Capsules: Box of 30.
Pregaforte®100: Capsules: Box of 30.
Pregaforte®150: Capsules: Box of 30.

COMPOSITION
Pregaforte® 25: Each capsule contains Pregabalin 25mg.
Excipients: lactose, starch, talc, magnesium stearate, titanium dioxide, gelatin, erythrosin, indigotine, black iron oxide.
Pregaforte® 75: Each capsule contains Pregabalin 75mg.
Excipients: lactose, starch, talc, magnesium stearate, gelatin, titanium dioxide, erythrosin, indigotine.
Pregaforte® 100: Each capsule contains Pregabalin 100mg.
Excipients: lactose, starch, talc, magnesium stearate, gelatin, titanium dioxide, erythrosin, sunset yellow, brilliant blue.
Pregaforte® 150: Each capsule contains Pregabalin 150mg.
Excipients: lactose, starch, talc, gelatin, titanium dioxide, brilliant blue, erythrosin.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Therapeutic class: Antiepileptics.
ATC code: N03AX16.
The active substance, Pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(amino-methyl)-5-methylhexanoic acid).
Pregabalin binds to an auxiliary subunit (α_2-ð protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.
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 hr 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 hrs. 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 hrs. 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 racemization 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 hrs. Pregabalin plasma clearance and renal clearance are directly proportional to Cl_{cr}.
Dosage adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.
Pharmacokinetics in special patient groups:
Renal impairment: Pregabalin clearance is directly proportional to Cl_{cr}. In addition, Pregabalin is effectively removed from plasma by haemodialysis (following a 4 hr haemodialysis treatment plasma Pregabalin concentrations are reduced by approximately 50%). Because renal elimination is the major elimination pathway, dosage reduction in patients with renal impairment and dosage 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 (> 65 years): Pregabalin clearance tends to decrease with increasing age. This decrease in Pregabalin oral clearance is consistent with decreases in Cl_{cr} associated with increasing age. Reduction of Pregabalin dose may be required in patients who have age related compromised renal function.

INDICATIONS
Neuropathic pain: Pregaforte® is indicated for the treatment of peripheral and central neuropathic pain in adults.
Epilepsy: Pregaforte® is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
Generalised Anxiety Disorder: Pregaforte® is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

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

PRECAUTIONS
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. There have also been post marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients
Cases of renal failure have been reported and discontinuation of Pregabalin did show reversibility of this adverse effect.
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, diarrhoea, flu syndrome, nervousness, depression, pain, sweating and dizziness. The patient should be informed about this at the start of the treatment.
There have been post-marketing reports of congestive heart failure in some patients receiving Pregabalin.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for Pregabalin.
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 medication affects their ability to perform these activities.

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. Pregabalin should not be used during pregnancy unless clearly necessary (if 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.

DRUG INTERACTIONS
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 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 medications. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

ADVERSE EFFECTS
The Pregabalin clinical programme involved over 9000 patients who were exposed to Pregabalin, of whom over 5000 were in double-blind placebo controlled trials. 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.
Below are mentioned all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency: Very common (> 1/10), common (> 1/100, < 1/10), uncommon (>1/1000, <1/100) and rare (<1/1000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
• **Immune system disorders:** Unknown frequency: Hypersensitivity, angioedema, allergic reaction
• **Blood and lymphatic system disorders:** Rare: Neutropenia
• **Metabolism and Nutrition disorders:** Common: Apetite increased; Uncommon: Anorexia; Rare: Hypoglycaemia
• **Psychiatric disorders:** Common: Euphoric mood, confusion, irritability, libido decreased; Uncommon: Hallucination, panic attack, restlessness, agitation, depression, depressed mood, mood swings, depersonalisation, insomnia exacerbated, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy; Rare: Disinhibition, elevated mood
• **Nervous system disorders:** Very common: Dizziness, somnolence; Common: Ataxia, coordination abnormal, tremor, dysarthria, memory impairement, disturbance in attention, paraesthesia; 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; Unknown frequency: Loss of consciousness, mental impairement, headache
• **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; Unknown frequency: Vision loss, keratitis
• **Ear and labyrinth disorders:** Common: Vertigo; Rare: Hyperacusis
•**Cardiac disorders:** Uncommon: Tachycardia; Rare: Atrioventricular block first degree, sinus tachycardia, sinus bradycardia, sinus arrhythmia; Unknown frequency: Congestive heart failure
• **Vascular disorders:** Unknown: Flushing, hot flushes; Rare: Hypotension, hypertension, peripheral coldness
• **Respiratory, thoracic and mediastinal disorders:** Uncommon: Dyspnoea, nasal dryness; Rare: Epistaxis, throat tightness, nasopharyngitis, cough, nasal congestion, rhinitis, snoring
• **Gastrointestinal disorders:** Common: Vomiting, dry mouth, constipation, flatulence; Uncommon: abdominal distension, gastrooesophageal reflux disease, salivary hypersecretion, oral hypoaesthesia; Rare: ascites, pancreatitis, dysphagia; Unknown frequency: swallen toungue, diarrhoea, nausea
• **Skin and subcutaneous tissue disorders:** Uncommon: Rash papular sweating; Rare: urticaria, cold sweat; Unknown frequency: Steven Johnson syndrom, 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; Unknown frequency: 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 periheral, oedema; Uncommon: fall, chest tightness, asthenia, thirst; Rare: Anasarca, pyrexia, rigors, pain exacerbated; Unknown frequency: Face oedema

DOSAGE AND ADMINISTRATION
The dose range is 150-600 mg/day given in either two or three divided doses. Pregaforte® may be taken with or without food.
Neuropathic pain: Pregaforte® treatment can be started at a dose of 150 mg/day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg/day after an interval of 3-7 days, and if needed, to a maximum dose of 600 mg/day after an additional 7-day interval.
Epilepsy: Pregaforte® treatment can be started with a dose of 150 mg/day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg/day after 1 week. The maximum dosage of 600 mg/day may be achieved after an additional week.
Generalised Anxiety Disorder: The dose range is 150-600 mg/day given as two or three divided doses. The need for treatment should be reassessed regularly.
Pregaforte® treatment can be started with a dose of 150 mg/day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg/day after 1 week. Following an additional week the dosage may be increased to 450 mg/day. The maximum dosage of 600 mg/day may be achieved after an additional week.
Discontinuation of Pregaforte®: In accordance with current clinical practice, if Pregaforte® has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication.
Children and adolescents: Pregaforte® 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.
Elderly (> 65 years): Elderly patients may require a dose reduction of Pregaforte® due to a decreased renal function.
Hepatic impairment: No dosage adjustment is required for patients with hepatic impairment.
Renal impairment: Pregaforte® is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As Pregaforte® clearance is directly proportional to Cl_{cr}, dosage reduction in patients with compromised renal function must be individualised according to Cl_{cr}, as indicated in Table 1.
Pregaforte® is removed effectively from plasma by haemodialysis (50% of drug in 4 hrs). For patients receiving haemodialysis, the Pregaforte®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-hr haemodialysis treatment (see Table 1).
Table 1. Pregaforte® dosage adjustment based on renal function

Cl_{cr} (ml/min)	Total Pregaforte® 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

OVERDOSAGE
In overdoses up to 15 g, no unexpected adverse reactions were reported. In the post-marketing experience, the most commonly reported adverse events 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.

STORAGE CONDITIONS
Store below 30°C.
Keep in original pack in intact conditions.

Date of revision: May 2018

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

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