

Aw. No.: 2000XXXXX

Front

Prezel Leaflet

Back

2000XXXXX

PREZEL 75 (PREGABALIN CAPSULES 75MG)
PREZEL 150 (PREGABALIN CAPSULES 150MG)

COMPOSITION:
Prezel 75 (Pregabalin Capsules 75mg)
Each hard gelatin capsule contains Pregabalin.....75mg
Excipients.....q.s.
Approved colours used in capsule shell

Prezel 150 (Pregabalin Capsules 150mg)
Each hard gelatin capsule contains Pregabalin.....150mg
Excipients.....q.s.
Approved colours used in capsule shell

PRESENTATION:
Prezel 75 (Pregabalin Capsule 75mg):
Size 4' hard gelatin capsules, reddish brown cap with creamish colour body.

Prezel 150 (Pregabalin Capsule 150mg):
Size 2' hard gelatin capsules, creamish cap with creamish colour body.

CLINICAL PHARMACOLOGY:
PHARMACODYNAMICS
Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics 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.

PHARMACOKINETICS
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_b by approximately 25-30% and a delay in t_{1/2} to approximately 2.5 max max 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 (Please refer table 1 of dose adjustment based on renal function).
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.
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 (Please refer table 1 of dose adjustment based on renal function).
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 (Please refer table 1 of dose adjustment based on renal function).
Breast-feeding mothers
Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma.

INDICATIONS
Neuropathic pain
Pregabalin is indicated for the treatment of peripheral and central 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 (GAD) in adults.
Fibromyalgia
Pregabalin is indicated for the management of fibromyalgia.

DOSAGE AND ADMINISTRATION
The dose range is 150 to 600 mg per day given in either two or three divided doses. Pregabalin may be taken with or without food.
Neuropathic pain: Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage 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.
Fibromyalgia: The usual dose range for most patients is 300 to 450 mg per day given in two divided doses. Some patients may derive additional benefit at 600 mg per day. Dosing should begin at 75 mg two times a day (150 mg/day) and 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). If needed, in some patients, based on individual response and tolerability, the dose may be increased to maximum dosage of 600 mg/day after an additional week.
Epilepsy: Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. The maximum dosage 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 dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week.
Discontinuation of pregabalin: If pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.
Patients with renal impairment: Dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{Cr}) (see Pharmacology: Pharmacokinetics: Pharmacokinetics in special patient groups: Renal impairment under Actions), as indicated in Table 1 determined using the following formula:

$$CL_{Cr} \left(\frac{mL}{min} \right) = \frac{[140 - age (years)] \times weight (kg)}{72 \times serum \text{ creatinine } \left(\frac{mg}{dL} \right)} \quad (x 0.85 \text{ for female patients})$$

For patients receiving hemodialysis, 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).

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 dosage following haemodialysis (mg)			
25			Single dose [†]

TID: Three divided doses BID: Two divided doses QD: Single daily dose
* 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 dosage adjustment is required for patients with hepatic impairment.
Use in children and adolescents (12 to 17 years of age): The safety and effectiveness of pregabalin in pediatric patients below the age of 12 years and adolescents has 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 decreased renal function

ROUTE OF ADMINISTRATION
Oral

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

WARNINGS AND PRECAUTIONS
Diabetic patients
Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic 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.



Pharmacode	No.
Front	3668
Back	3669

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Dimension: 160 x 300mm

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Pharmacode	No.
Front 	3668
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Item Code No.	2000XXXXX		Revision No.:	01		
			Prev. Aw. No.:	200010363		
Packaging Development	Marketing	R & D / Regulatory	Production	Quality Control	Quality Assurance	Party Approval

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, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

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.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled studies 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. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

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).

Misuse, abuse potential or dependence
Cases of misuse, abuse and dependence 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 misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported).
Encephalopathy
Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy
Potential for an increase in risk of suicidal thoughts or behaviors

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.

Population pharmacokinetic analysis
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.
CNS influencing medicinal products
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.
Interactions and the elderly
No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults

PREGNANCY AND LACTATION
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.
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. Pregabalin Capsules should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).
Breast-feeding
Pregabalin is excreted into human milk. The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no clinical data on the effects of pregabalin on female fertility.
SIDE EFFECTS
The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In table 2 below 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; common; uncommon; rare; very rare, not known. 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. Additional reactions reported from postmarketing experience are included in italics in the list below.

System Organ Class	Adverse drug reactions
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropenia
Immune system disorders	
Uncommon	<i>Hypersensitivity</i>
Rare	<i>Angioedema, allergic reaction</i>
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition
Nervous system disorders	
Very Common	Dizziness, somnolence, headache
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, stupor, myoclonus, <i>loss of consciousness</i> , psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, <i>mental impairment</i> , speech disorder, hyporeflexia, hyperaesthesia, burning sensation, agnosia, <i>malaise</i>
Rare	<i>Convulsions</i> , paranoia, hypokinesia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual field disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	<i>Vision loss, keratitis</i> , oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, <i>congestive heart failure</i>
Rare	<i>QT prolongation</i> , sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flashes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	<i>Pulmonary oedema</i> , throat tightness
Gastrointestinal disorders	
Common	Vomiting, <i>nausea</i> , constipation, <i>diarrhoea</i> , flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoesthesia oral
Rare	Ascites, pancreatitis, <i>swollen tongue</i> , dysphagia
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, hyperhidrosis, <i>pruritus</i>
Rare	<i>Stevens-Johnson syndrome</i> , cold sweat
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, <i>urinary retention</i>
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, <i>gynaecomastia</i>
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, <i>face oedema</i> , chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

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

Concerning discontinuation of long-term treatment of pregabalin, the incidence and severity of withdrawal symptoms may be dose-related.
Paediatric population
The most common adverse events were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis.

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. Seizures were also reported. In rare occasions, cases of coma have been reported. Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Prezel may have minor or moderate influence on the ability to drive and use machines. Prezel 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.

STORAGE CONDITION
Store below 30°C.
PACK SIZE
Blister pack of 10 capsules. Such 3 blisters of 10 Capsules each are packed in a carton along with insert.

PRODUCT REGISTRATION HOLDER
Synetrv Sdn Bhd, SO-29-2, Menara 1, K1 Eco City, Jalan Bangsar, Kg Haji Abdullah Hukum, 59200 Kuala Lumpur, Malaysia

KEEP ALL MEDICINES OUT OF REACH AND SIGHT OF CHILDREN
Manufactured by :
 **Ind-Swift Laboratories Limited**
Off- NH-21, Village Jawaharpur,
Telshi Derabassi, Dist. S.A.S Nagar
Ind-Swift
Laboratories Limited
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