Hilin®
(Pregabalin)

Highnoon

COMPOSITION
Hilin 50mg Capsule:
Each capsule contains: Pregabalin 50mg
Hilin 75mg Capsule:
Each capsule contains: Pregabalin 75mg
Hilin 100mg Capsule:
Each capsule contains: Pregabalin 100mg
Hilin 150mg Capsule:
Each capsule contains: Pregabalin 150mg

DESCRIPTION
Hilin (Pregabalin) is a structural derivative of the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA).

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 has not been fully elucidated, but it is suggested that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animals. In animal models of nerve damage, pregabalin has been shown to reduce calcium-dependent release of pro-nociceptive neurotransmitters in the spinal cord, possibly by disrupting alpha2-delta containing-calcium channel trafficking and/or reducing calcium currents. The anti-nociceptive activities of pregabalin may also be mediated through interactions with descending noradrenergic and serotonergic pathways originating from the brainstem that modulate pain transmission in the spinal cord.

PHARMACOKINETICS
Pregabalin is rapidly absorbed after oral doses and peak plasma concentrations occur within 1.5 hours. Oral bioavailability is about 90%. The rate but not the extent of absorption is reduced if given with food but this is not clinically significant. Pregabalin is not bound to plasma proteins and undergoes negligible metabolism. About 98% of the dose is excreted in the urine as unchanged drug. The mean elimination half-life is 6.3 hours. Pregabalin is removed by hemodialysis.

INDICATIONS AND USAGE
It is indicated for:
- Management of neuropathic pain associated with diabetic peripheral neuropathy
- Management of postherpetic neuralgia
- Adjunctive therapy for the treatment of partial onset seizures in patients 1 month of age and older
- Management of fibromyalgia
- Management of neuropathic pain associated with spinal cord injury

DOSAGE AND ADMINISTRATION
- It is given orally with or without food. When discontinuing it, taper gradually over a minimum of 1 week. Because pregabalin is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function.
- In neuropathic pain associated with diabetic peripheral neuropathy the maximum recommended dose of Pregabalin is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60mL/min. Begin dosing at 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. In dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended.
- In Postherpetic Neuralgia the recommended dose is 75 to 150 mg two times a day, or 50 to 100 mg three times a day (150 to 300 mg/day) in patients with creatinine clearance of at least 60 mUmin. Begin dosing at 75 mg two times a day, or 50 mg three times a day (150 mg/day). The dose may be increased to 300 mg/day within 1 week based on efficacy and tolerability. Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with 300 mg/day, and who are able to tolerate it , may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day).
- In adjunctive therapy for partial onset seizures in patients 1 month of age and older the recommended dosage for adults and paediatric patients 1 month of age and older is included in below table. Administer the total daily dosage orally in two or three divided doses. In paediatric patients. the recommended dosing regimen is dependent upon body weight. Based on clinical response and tolerability, dosage may be increased, approximately weekly.

Recommended Dosage for Adults and Paediatric Patients 1 montht and Older

Age and Body Weight	Recommended Initial Dosage (Administer in two or three divided doses)	Recommended Maximum Dosage (Administer in two or three divided doses)	Frequency of administration
Adults (17 years and older)	150 mg/day	600 mg/day	2 or 3 divided doses
Pediatric patients weighing 30 kg or more	2.5 mg/kg/day	10 mg/kg/day (Not to exceed 600 mg/day)	2 or 3 divided doses
Pediatric patients weighing 11 kg to less than 30 kg	3.5 mg/kg/day	14 mg/kg/day	1 month to less than 4 years of age; 3 divided doses 4 years of age and older; 2 or 3 divided doses

- In the management of Fibromyalgia, the recommended dose 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). In dose-dependent adverse reactions, treatment with doses above 450 mg/day is not recommended.
- The recommended dose range for the treatment of neuropathic pain associated with spinal cord injury is 150 to 600 mg/day. The recommended starting dose is 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 pain relief after 2 to 3 weeks of treatment with 150 mg two times a day and who tolerate it, may be treated with up to 300 mg two times a day.
- For adult patients with renal impairment, in view of dose dependent adverse reactions and since pregabalin is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function. The use of pregabalin in pediatric patients with compromised renal function has not been studied.
- For patients undergoing hemodialysis, adjust the pregabalin daily dose based on renal function. In addition to the daily dose adjustment, administer a supplemental dose immediately following every 4-hour hemodialysis treatment as mentioned in below able.

Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CrCl) (mL/min)	Total Pregabalin Daily Dose (mg/day)*				Dose Regimen
Greater than or equal to 60	150	300	450	600	BID or TID
30-60	75	150	225	300	BID or TID
15-30	25-50	75	100-150	150	QD or BID
Less than 15	25	25-50	50-75	75	QD

Supplementary dosage following hemodialysis (mg) †

Patients on the 25 mg QD regimen:
Take one supplemental dose of 25 mg or 50mg

Patients on the 25-50 mg QD regimen:
Take one supplemental dose of 50 mg or 75 mg

Patients on the 50-75 mg QD regimen:
Take one supplemental dose of 75 mg or 100 mg

Patients on the 75 mg QD regimen:
Take one supplemental dose of 100 mg or 150 mg

TID = Three divided doses; BIO= Two divided doses; QO = 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.

CONTRAINDICATIONS
It is contraindicated in patients with known hypersensitivity to pregabalin or any of its components. Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

WARNINGS AND PRECAUTIONS
- There have been reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Discontinue pregabalin immediately in patients with these symptoms. Exercise caution when prescribing pregabalin to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors (ACE-inhibitors]) may be at increased risk of developing angioedema.
- There have been reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue pregabalin immediately in patients with these symptoms.
- As with all antiepileptic drugs (AEDs), withdraw pregabalin gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperttiidrosis, and diarrhoea. If pregabalin is discontinued, taper the drug gradually over a minimum of 1 week rather than discontinue the drug abruptly.
- Antiepileptic drugs (AEDs), including pregabalin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with any AEO for any indication for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour. Anyone considering prescribing pregabalin or any other AED must balance the risk of suicidal thoughts or behaviour with the risk of untreated illness. Epilepsy and many other illnesses for which AEOs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
- Pregabalin treatment may cause peripheral edema. There was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. Higher frequencies of weight gain and peripheral edema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering pregabalin and these agents. There are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients.
- Pregabalin may cause dizziness and somnolence. Inform patients that pregabalin -related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery.
- Pregabalin treatment may cause weight gain. Pregabalin associated weight gain was related to dose and duration of exposure but did not appear to be associated with baseline BMI, gender, or age. Weight gain was not limited to patients with edema.
- An unexpectedly high incidence of hemangiosarcoma was identified in animals. The clinical significance of this finding is unknown.
- A higher proportion of patients treated with pregabalin reported blurred vision which resolved in a majority of cases with continued dosing. Although the clinical significance of the ophthalmologic findings is unknown, inform patients to notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions.
- Pregabalin treatment was associated with creatine kinase elevations. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment with pregabalin if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.
- Pregabalin treatment was associated with a decrease in platelet count.
- Pregabalin treatment was associated with PR interval prolongation.
- There is evidence of serious life threatening or fatal respiratory depression when co-administered with Central Nervous System (CNS) depressants including opioids, or in the setting of underlying respiratory impairemnt. When the decision is made to co-prescribe pregabalin with another CNS depressant particularly an opioid or to prescribe pregabalin to patients with underlying respiratory impairment, monitor the patients for symptoms of respiratory depression and sedation, and consider initiating pregabalin at a lower dose. The management of respiratory depression may include close observation, supportive measures and reduction or withdrawal of CNS depressant (including pregabalin).

ADVERSE REACTIONS
The most common reported adverse events are angioedema, hypersensitivity, increased risk of adverse reactions with abrupt or rapid discontinuation, suicidal behaviour and ideation, peripheral edema, dizziness, somnolence, weight gain, tumorigenic potential, ophthalmological effects, creatine kinase elevations, decreased platelet count, respiratory depression, PR interval prolongation, abdominal pain, allergic reaction, fever, gastroenteritis, increased appetite, ecchymosis, arthralgia, leg cramps, myalgia, myasthenia, anxiety, depersonalization, hypertonia, hypoesthesia, libido decreased, nystagmus, paresthesia, sedation, stupor, twitching, pruritus, conjunctivitis, diplopia, otitis media, tinnitus, anorgasmia, impotence, urinary frequency and urinary incontinence.

The infrequently reported adverse events are; abscess, cellulitis, chills, malaise, neck rigidity, overdose, pelvic pain, photosensitivity reaction, deep thrombophlebitis, heart failure, hypotension, postural hypotension, retinal vascular disorder, syncope, cholecystitis, cholelithiasis, colitis, dysphagia, esophagitis, gastritis, gastrointestinal haemorrhage, melena, mouth ulceration, pancreatitis, rectal haemorrhage, tongue edema, anaemia, eosinophilia, hypochromic anaemia, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia, arthrosis, abnormal dreams, agitation, apathy, aphasia, circumoral paresthesia, dysarthria, hallucinations, hostility, hyperalgesia, hyperesthesia, hyperkinesia, hypokinesia, hypotonia, libido increased, myoclonus, neuralgia, alopecia, dry skin, eczema, hirsutism, skin ulcer, urticaria, vesiculobullous rash, abnormality of accommodation, blepharitis, dry eyes, eye haemorrhage, hyperacusis, photophobia, retinal edema, taste loss, taste perversion, abnormal ejaculation, albuminuria, amenorrhea, dysmenorrhea, dysuria, hematuria, kidney calculus, leukorrhea, menorrhagia, metrorrhagia, nephritis, oliguria, urinary retention and urine abnormality.

The rarely reported events are: anaphylactoid reaction, ascites, granuloma, hangover effect, intentional injury, retroperitoneal fibrosis, shock, ST depressed, ventricular fibrillation, aphthous stomatitis, esophageal ulcer, periodontal abscess, myelofibrosis, polycythemia, prothrombin decreased, purpura, thrombocythemia, alanine aminotransferase increased, aspartate aminotransferase increased, glucose tolerance decreased, urate crystalluria, chondrodystrophy, generalized spasm, addiction, cerebellar syndrome, cogwheel rigidity, coma, delirium, delusions, dysautonomia, dyskinesia, dystonia, encephalopathy, extrapyramidal syndrome, Guillain-Barre syndrome, hypoalgesia, intracranial hypertension, manic reaction, paranoid reaction, peripheral neuritis, personality disorder, psychotic depression, schizophrenic reaction, sleep disorder, torticollis, trismus, apnea, atelectasis, bronchiolitis, hiccup, laryngismus, lung edema, lung fibrosis, yawn, angioedema, exfoliative dermatitis, lichenoid dermatitis, melanosis, nail disorder, petechial rash, purpuric rash, pustular rash, skin atrophy, skin necrosis, skin nodule, Stevens Johnson Syndrome, subcutaneous nodule, anisocoria, blindness, corneal ulcer, exophthalmos, extraocular palsy, iritis, keratitis, keratoconjunctivitis, miosis, mydriasis, night blindness, ophthalmoplegia, optic atrophy, papilledema, parosmia, ptosis, uveitis, acute kidney failure, balanitis, bladder neoplasm, cervicitis, dyspareunia, epididymitis, female lactation, glomerulitis, ovarian disorder and pyelonephritis.

The other reported adverse events are; headache, nausea, diarrhoea, gynecomastia, breast enlargement, reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation), reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications, ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, dry mouth, edema, accidental injury, back pain, chest pain, flatulence, hypoglycemia, vertigo, neuropathy, euphoria, abnormal gait, amnesia, nervousness, dyspnea, pain, infection, flu syndrome, vomiting, speech disorder, bronchitis, tremor, worsening of epilepsy, salivary hypersecretion, abdominal distention, fatigue, sinusitis, fluid retention, memory impairment, lethargy, disorientation, pharyngolaryngeal pain, nasopharyngitis, muscular weakness, pain in extremity, neck pain, joint swelling, insomnia, decubitus ulcer, erectile dysfunction, pneumonia, face oedema, viral infection and hypertension.

DRUG INTERACTIONS
Pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (less than 2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. There are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs. No pharmacokinetic interactions were seen, when pregabalin co-administered with oxycodone, lorazepam, or ethanol.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no adequate and well-controlled studies with pregabalin in pregnant women. Advise pregnant women of the potential risk to a fetus.

Lactation
Small amounts of pregabalin have been detected in the milk of lactating women. Because of the potential risk of tumorigenicity, breastfeeding is not recommended during treatment with pregabalin.

Females and Males of Reproductive Potential
Effects on Spermatogenesis; In the animal fertility study with pregabalin in male rats, adverse reproductive and developmental effects were observed.

Paediatric Use
The safety and effectiveness in paediatric patients have not been established for Neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and neuropathic pain associated with spinal cord injury.

The safety and effectiveness in paediatric patients have not been established for fibromyalgia.

The safety and effectiveness in patients below the age of 1 month have not been established for adjunctive therapy for partial onset seizures.

Geriatric Use
No overall differences in safety and efficacy were observed between older patients and younger patients. Pregabalin is known to be substantially excreted by the kidney, and the risk of toxic reactions to pregabalin may be greater in patients with impaired renal function. Because pregabalin is eliminated primarily by renal excretion, adjust the dose for elderly patients with renal impairment.

Renal Impairment
Pregabalin is eliminated primarily by renal excretion and dose adjustment is recommended for adult patients with renal impairment. The use of pregabalin in pediatric patients with compromised renal function has not been studied.

DRUG ABUSE AND DEPENDENCE
Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour). Abrupt or rapid discontinuation of pregabalin, the reported symptoms including insomnia, nausea, headache or diarrhoea consistent with physical dependence. There have also been reported cases of anxiety and hyperhidrosis.

OVERDOSAGE
There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observe usual precautions to maintain the airway. General supportive ca.re of the patient is indicated inducing monitoring of vita. l signs and observation of the clinical status of the patient. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Hilin 50mg Capsules: Alu. PVC. Blister Pack of 2 x 7's.
Hilin 75mg Capsules: Alu. PVC. Blister Pack of 2 x 7's.
Hilin 100mg Capsules: Alu. PVC. Blister Pack of 2 x 7's.
Hilin 150mg Capsules: Alu. PVC. Blister Pack of 2 x 7's.

ہائیلِن®
(پری گابالِن)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

Item Code No. 14002635