Gabolest® Capsules
(pregabalin)

گیبولسٹ

QUALITATIVE AND QUANTITATIVE COMPOSITION
Gabolest® Capsules 25 mg
Each capsule contains:
Pregabalin U.S.P. .....25 mg
Gabolest® Capsules 50 mg
Each capsule contains:
Pregabalin U.S.P. .....50 mg
Gabolest® Capsules 75 mg
Each capsule contains:
Pregabalin U.S.P. .....75 mg
Gabolest® Capsules 100 mg
Each capsule contains:
Pregabalin U.S.P. .....100 mg
Gabolest® Capsules 150 mg
Each capsule contains:
Pregabalin U.S.P. .....150 mg
Gabolest® Capsules 300 mg
Each capsule contains:
Pregabalin U.S.P. .....300 mg

INDICATIONS AND USAGE
Gabolest® is indicated for management of
1. Neuropathic pain associated with diabetic peripheral neuropathy
2. Postherpetic neuralgia
3. Adjunctive therapy for the treatment of partial onset seizures in patients 4 years of age and older
4. Fibromyalgia
5. Neuropathic pain associated with spinal cord injury

DOSAGE AND ADMINISTRATION
Gabolest® is given orally with or without food.
When discontinuing Gabolest®, taper gradually over a minimum of 1 week.

1. Neuropathic Pain Associated with Diabetic Peripheral Neuropathy: The maximum recommended dose of Gabolest® is 100 mg three times a day (300 mg/day) in patients with creatinine clearance of at least 60 mL/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. Because Gabolest® is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

Although Gabolest® was also studied at 600 mg/day, there is no evidence that this dose confers additional significant benefit and this dose was less well tolerated. In view of the dose-dependent adverse reactions, treatment with doses above 300 mg/day is not recommended.

2. Postherpetic Neuralgia: The recommended dose of Gabolest® 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 mL/min. 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. Because Gabolest® is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

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 Gabolest®, may be treated with up to 300 mg two times a day, or 200 mg three times a day (600 mg/day). In view of the dose-dependent adverse reactions and the higher rate of treatment discontinuation due to adverse reactions, reserve dosing above 300 mg/day for those patients who have on-going pain and are tolerating 300 mg daily.

Adjunctive Therapy for Partial Onset Seizures in Patients 4 Years of Age and Older: The recommended dosage for adults and pediatric patients 4 years of age and older is included in Table 1. Administer the total daily dosage orally in two or three divided doses. In pediatric patients 4 years of age and older, the recommended dosing regimen is dependent upon body weight. Based on clinical response and tolerability, dosage may be increased, approximately weekly.

Table 1: Recommended Dosage for Adults and Pediatric Patients 4 Years 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)
Adults (17 years and older)	150 mg/day	600 mg/day
Pediatric patients weighing 30 kg or more	2.5 mg/kg/day	10 mg/kg/day (not to exceed 600 mg/day)
Pediatric patients weighing 11 kg to less than 30 kg	3.5 mg/kg/day	14 mg/kg/day

The effect of dose escalation rate on the tolerability of Gabolest® has not been formally studied.

The efficacy of add-on Gabolest® in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of Gabolest® with gabapentin cannot be offered.

4. Management of Fibromyalgia: The recommended dose of Gabolest® 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 Gabolest® 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 Gabolest® is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

5. Neuropathic Pain Associated with Spinal Cord Injury: The recommended dose range of Gabolest® 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 Gabolest® may be treated with up to 300 mg two times a day. Because Gabolest® is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function.

6. Patients with Renal Impairment: In view of dose-dependent adverse reactions and since Gabolest® is eliminated primarily by renal excretion, adjust the dose in patients with reduced renal function. The use of pregabalin in pediatric patients with compromised renal function has not been studied. Base the dose adjustment in patients with renal impairment on creatinine clearance (CLcr), as indicated in Table 2. To use this dosing table, an estimate of the patient's CLcr in mL/min is needed. CLcr in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$\text{CLCr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Next, refer to the Dosage and Administration section to determine the recommended total daily dose based on indication, for a patient with normal renal function (CLcr greater than or equal to 60 mL/min). Then refer to Table 1 to determine the corresponding renal adjusted dose.
(For example: A patient initiating Gabolest® therapy for postherpetic neuralgia with normal renal function (CLcr greater than or equal to 60 mL/min), receives a total daily dose of 150 mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50 mL/min would receive a total daily dose of 75 mg/day pregabalin administered in two or three divided doses.)
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 (see Table 2).

Table 2. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	Total Pregabalin Daily Dose (mg/day)*				Dose Regimen
≥ 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
<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 50 mg 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; 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.

CONTRAINDICATIONS

Gabolest® 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

Angioedema: There have been postmarketing reports of angioedema in patients during initial and chronic treatment with Gabolest®. 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 Gabolest® immediately in patients with these symptoms.

Exercise caution when prescribing Gabolest® 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.

Hypersensitivity: There have been postmarketing reports of hypersensitivity in patients shortly after initiation of treatment with Gabolest®. Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue Gabolest® immediately in patients with these symptoms.

Withdrawal of Antiepileptic Drugs (AEDs): As with all AEDs, Gabolest® should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If Gabolest® is discontinued this should be done gradually over a minimum of 1 week.

Suicidal Behavior and Ideation: Antiepileptic drugs (AEDs), including Gabolest®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono-and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed.

Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3. Risk by indication for antiepileptic drugs in the pooled analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications

Anyone considering prescribing Gabolest® or any other AED

must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior 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. Inform patients, their caregivers, and families that Gabolest® and other AEDs increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers.

Peripheral Edema: Gabolest® treatment may cause peripheral edema. In short term trials of patients without clinically significant heart or peripheral vascular disease, 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.

In controlled clinical trials the incidence of peripheral edema was 6% in the Gabolest® group compared with 2% in the placebo group. In controlled clinical trials, 0.5% of Gabolest® patients and 0.2% placebo patients withdrew due to peripheral edema.
Higher frequencies of weight gain and peripheral edema were observed in patients taking both Gabolest® and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with Gabolest® only, and 19% (23/120) of patients who were on both Gabolest® and thiazolidinedione anti-diabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on Gabolest® only; and 7.5% (9/120) of patients on both drugs.

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 Gabolest®and these agents.

Because 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 Gabolest® in these patients.

Dizziness and Somnolence: Gabolest® causes dizziness and somnolence. Patients should be informed that Gabolest®-related dizziness and somnolence may impair their ability to perform task such as driving or operating machinery.

In the Gabolest® controlled trials, dizziness was experienced by 30% of Gabolest® treated patients compared to 8% of placebo-treated patients; somnolence was experienced by 23% of Gabolest®-treated patients compared to 8% of placebo-treated patients. Dizziness and somnolence generally began shortly after the initiation of Gabolest® therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse events most frequently leading to withdrawal (4% each) from controlled studies. In Gabolest®-treated patients reporting these adverse events in short-term, controlled studies, dizziness persisted until the last dose in 30% and somnolence persisted until the last dose in 42% of patients.

Weight Gain: Gabolest® treatment caused weight gain. In Gabolest® controlled clinical trials of up to 14 weeks, a gain of 7% or more over baseline weight was observed in 9% of Gabolest® treated patients and 2% of placebo-treated patients. Few patients treated with Gabolest® (0.3%) withdrew from controlled trials due to weight gain. Gabolest® 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.

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of Gabolest®-associated weight gain are unknown.

Among diabetic patients, Gabolest®-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received Gabolest® for at least 2 years, the average weight gain was 5.2 kg.
While the effects of Gabolest®-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, Gabolest® treatment did not appear to be associated with loss of glycemic control (as measured by HbA1C).

Abrupt or Rapid Discontinuation: Following abrupt or rapid discontinuation of Gabolest®, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea. Gabolest® should be tapered gradually over a minimum of 1 week rather than discontinued abruptly.

Tumorigenic Potential: In standard preclinical in vivo lifetime carcinogenicity studies of Gabolest®, an unexpectedly high incidence of hemangiosarcoma was identified in two different strains of mice. The clinical significance of this finding is unknown. Clinical experience during Gabolest®'s premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in patients >12 years of age, new or worsening-preexisting tumors were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with Gabolest®, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.
Ophthalmological Effects: In controlled studies, a higher proportion of patients treated with Gabolest® reported blurred vision (7%) than did patients treated with placebo (2%), which resolved in a majority of cases with continued dosing. Less than 1 % of patients discontinued Gabolest® treatment due to vision-related events (primarily blurred vision).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with Gabolest®, and 5% of placebo-treated patients. Visual field changes were detected in 13% of Gabolest®-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of Gabolest®-treated and 2% of placebo-treated patients.

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

Creatine Kinase Elevations: Gabolest® treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for Gabolest®-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 1.5% of patients on Gabolest® and 0.7% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three Gabolest® treated subjects had events reported as rhabdomyolysis in pre marketing clinical trials. The relationship between these myopathy events and Gabolest® is not completely understood because the cases had documented factors that may have caused or contributed to these events. 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 Gabolest® if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count: Gabolest® treatment was associated with a decrease in platelet count. Gabolest®-treated subjects experienced a mean maximal decrease in platelet count of 20 × 103/μL, compared to 11 × 103/μL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of Gabolest® patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 × 103/μL.
In randomized controlled trials, Gabolest® was not associated with an increase in bleeding-related adverse events.

PR Interval Prolongation: Gabolest® treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at Gabolest® doses greater than or equal to 300 mg/day. This mean change difference was not associated with an increased risk of PR increase greater than or equal to 25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block.

Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

ADVERSE REACTIONS

The pregabalin clinical program involved over 8900 patients exposed to pregabalin, of whom over 5600 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 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In table 3 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 (≥ 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.

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	Neutropaenia
Immune system disorders	
Uncommon	*Hypersensitivity*
Rare	*Angioedema, allergic reaction*
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, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon	Syncope, stupor, myoclonus, *loss of consciousness,* psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder,*mental impairment,* speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, *malaise*
Rare	*Convulsions,* parosmia, hypokinesia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	*Vision loss, keratitis,* 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, *congestive heart failure*
Rare	*QT prolongation,* sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness

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

The pregabalin safety profile observed in two paediatric studies (pharmacokinetic and tolerability study, n=65; 1 year open label follow on safety study, n=54) was similar to that observed in the adult studies

DRUG INTERACTIONS
Since Gabolest® is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<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. In vitro and in vivo studies showed that Gabolest® is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, 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 Gabolest® and commonly used antiepileptic drugs.

Pharmacodynamics
Multiple oral doses of Gabolest® were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when Gabolest® was co-administered with these drugs. No clinically important effects on respiration were seen

USE IN SPECIFIC POPULATIONS
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 and well-controlled studies with Gabolest® in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Gabolest® 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.
In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.

A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown.

Pediatric Use: The safety and efficacy of pregabalin in pediatric patients have not been established.

Geriatric Use: In controlled clinical studies of Gabolest® in neuropathic pain associated with
- diabetic peripheral neuropathy, 246 patients were 65 to 74 years of age, and 73 patients were 75 years of age or older.
- postherpetic neuralgia, 282 patients were 65 to 74 years of age, and 379 patients were 75 years of age or older.

In controlled clinical studies of Gabolest® in epilepsy, there were only 10 patients 65 to 74 years of age, and 2 patients who were 75 years of age or older.

No overall differences in safety and efficacy were observed between these patients and younger patients.

In controlled clinical studies of Gabolest® in fibromyalgia, 106 patients were 65 years of age or older. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy.

Gabolest® is known to be substantially excreted by the kidney, and the risk of toxic reactions to Gabolest® may be greater in patients with impaired renal function. Because Gabolest® is eliminated primarily by renal excretion, adjust the dose for elderly patients with renal impairment

OVERDOSAGE
Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans: There is limited experience with overdose of Gabolest®. The highest reported accidental overdose of Gabolest® during the clinical development program was 8000 mg, and there were no notable clinical consequences.
Treatment or Management of Overdose: There is no specific antidote for overdose with Gabolest®. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; observe usual precautions to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

PHARMACOLOGICAL PROPERTIES
Mechanism of Action
Gabolest® (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, results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's anti-nociceptive and antiseizure effects in animal models. 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. Evidence from other animal models of nerve damage and persistent pain suggest 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.

While pregabalin is a structural derivative of the inhibitory

neurotransmitter gammaaminobutyric acid (GABA), it does not bind directly to GABAA, GABAB, or benzodiazepine receptors, does not augment GABAA responses in cultured neurons, does not alter rat brain GABA concentration or have acute effects on GABA uptake or degradation. However, in cultured neurons prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not active at opiate receptors, and does not alter cyclooxygenase enzyme activity. It is inactive at serotonin and dopamine receptors and does not inhibit dopamine, serotonin, or noradrenaline reuptake.

Pharmacokinetics
Pregabalin is well absorbed after oral administration, is eliminated largely by renal excretion, and has an elimination half-life of about 6 hours.

Absorption and Distribution
Following oral administration of Gabolest® capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is >90% and is independent of dose. Following single-(25 to 300 mg) and multiple-dose (75 to 900 mg/day) administration, maximum plasma concentrations (Cmax) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data.

The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in Cmax of approximately 25% to 30% and an increase in Tmax to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.
Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier. Although there are no data in humans, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. In addition, pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats.

Metabolism and Elimination
Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 90% of the administered dose was recovered in the urine as 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, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits, or monkeys.

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug with a mean elimination half-life of 6.3 hours in subjects with normal renal function. Mean renal clearance was estimated to be 67.0 to 80.9 mL/min in young healthy subjects. Because pregabalin is not bound to plasma proteins this clearance rate indicates that renal tubular reabsorption is involved. Pregabalin elimination is nearly proportional to creatinine clearance (CLcr).

Pharmacokinetics in Special Populations
Race: In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of Gabolest® were not significantly affected by race (Caucasians, Blacks and Hispanics).

Gender: Population pharmacokinetic analyses of the clinical studies showed that the relationship between daily dose and Gabolest® drug exposure is similar between genders.

Renal Impairment and Hemodialysis: Pregabalin clearance is nearly proportional to creatinine clearance (CLcr). Dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified.
Elderly: Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in CLcr.
Reduction of pregabalin dose may be required in patients who have age-related compromised renal function.

Pediatric Pharmacokinetics: Pharmacokinetics of pregabalin has not been adequately studied in pediatric patients.

PHARMACEUTICAL PARTICULARS
Shelf Life: Observe expiry date on the outer pack.

Dosage And Instructions:
As prescribed by the physician.
Keep out of the reach of children.
Do not store above 30˚C. Protect from light and moisture.
To be sold on the prescription of a registered medical practitioner only.

خوراک و ہدایات :
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ بچوں کی پہنچ سے دور رکھیں۔
۳۰ ڈگری سینٹی گریڈ سے زیادہ درجۂ حرارت پر نہ رکھیں۔ دوا کو روشنی اور نمی سے بچائیں۔
صرف مستند ڈاکٹر کے نسخے پر فروخت کریں۔

Presentation
Gabolest® 25 mg (pregabalin) is supplied in blister pack of 2 X 7 capsules.
Gabolest® 50 mg (pregabalin) is supplied in blister pack of 2 X 7 capsules.
Gabolest® 75 mg (pregabalin) is supplied in blister pack of 2 X 7 capsules.
Gabolest® 100 mg (pregabalin) is supplied in blister pack of 2 X 7 capsules.
Gabolest® 150 mg (pregabalin) is supplied in blister pack of 2 X 7 capsules.
Gabolest® 300 mg (pregabalin) is supplied in blister pack of 2 X 7 capsules.

Manufactured by:

ASPIN
An OBS Group Company
Aspin Pharma (Pvt.) Ltd.
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