Averopreg

(Pregabalin)

Pharmaceutical forms:

- Averopreg 100 mg /5ml oral solution.
- Averopreg 100 mg Hard Gelatin Capsule.
- Averopreg 50 mg Hard Gelatin Capsule.

INDICATIONS AND USAGE:

Averopreg 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

1-Important Administration Instructions

Averopreg is given orally with or without food.

When discontinuing Averopreg, taper gradually over a minimum of 1 week *[see Warnings and Precautions]*.

Because Averopreg is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function *[see Dosage and Administration]*.

2- Neuropathic Pain Associated with Diabetic Peripheral Neuropathy in Adults

The maximum recommended dose of Averopreg 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.

Although Averopreg 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 *[see Adverse Reactions]*.

3- Postherpetic Neuralgia in Adults

The recommended dose of Averopreg 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.

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 Averopreg, 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 *[see Adverse Reactions]*.

4- Adjunctive Therapy for Partial-Onset Seizures in Patients 1 Month of Age and Older

The recommended dosages for adults and pediatric patients 1 month of age and older are included in Table 1. Administer the total daily dosage orally in two or three divided doses as indicated in Table 1. In pediatric patients, 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 1 Month and Older

Age and Body Weight	**Recommended Initial Dosage**	**Recommended Maximum Dosage**	**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 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

Both the efficacy and adverse event profiles of Averopreg have been shown to be dose-related.

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

The efficacy of adjunctive Averopreg in patients taking gabapentin has not been evaluated in controlled trials. Consequently, dosing recommendations for the use of Averopreg with gabapentin cannot be offered.

5-Management of Fibromyalgia in Adults

The recommended dose of Averopreg 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 Averopreg 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 *[see Adverse Reactions]*.

6- Neuropathic Pain Associated with Spinal Cord Injury in Adults

The recommended dose range of Averopreg 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 Averopreg may be treated with up to 300 mg two times a day.

7- Dosing for Adult Patients with Renal Impairment

In view of dose-dependent adverse reactions and since Averopreg is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function. The use of Averopreg 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:

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

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 2 to determine the corresponding renal adjusted dose.

(For example: A patient initiating Averopreg 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**
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	25-50	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.

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg, 100 mg.

Oral Solution: 100 mg / 5Ml.

CONTRAINDICATIONS

Averopreg 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 *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

1-Angioedema

There have been postmarketing reports of angioedema in patients during initial and chronic treatment with Averopreg. 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 Averopreg immediately in patients with these symptoms.

Exercise caution when prescribing Averopreg 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.

2- Hypersensitivity

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

3-Increased Risk of Adverse Reactions with Abrupt or Rapid Discontinuation

As with all antiepileptic drugs (AEDs), withdraw Averopreg gradually to minimize the potential of increased seizure frequency in patients with seizure disorders.

Following abrupt or rapid discontinuation of Averopreg, some patients reported symptoms including insomnia, nausea, headache, anxiety, hyperhidrosis, and diarrhea.

If Averopreg is discontinued, taper the drug gradually over a minimum of 1 week rather than discontinue the drug abruptly.

4- Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Averopreg, 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.

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.

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 Averopreg 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.

5- Peripheral Edema

Averopreg 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.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both Averopreg 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.

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 Averopreg 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 Averopreg in these patients.

6- Dizziness and Somnolence

Averopreg may cause dizziness and somnolence. Inform patients that Averopreg -related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery *[see Patient Counseling Information]*.

For patients 1 month to less than 4 years of age, somnolence includes related terms lethargy, sluggishness, and hypersomnia.

7- Weight Gain

Averopreg treatment may cause weight gain. Averopreg 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 *[see Warnings and Precautions]*.

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

While the effects of Pregabalin -associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, Averopreg treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1C}).

8- Tumorigenic Potential

In standard preclinical *in vivo* lifetime carcinogenicity studies of Pregabalin, 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 Pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

9- Ophthalmological Effects

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 *[see Patient Counseling Information]*.

10- Creatine Kinase Elevations

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 Averopreg if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

11- Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count.

12-PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation.

13-Sodium metabisulfite

Sodium metabisulfite in Averopreg Solution that may cause allergic-type reactions including anaphylactic symptoms and life threatening or less severe asthmatic episodes in certain susceptible people. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people."

14-Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Adverse REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Angioedema *[see Warnings and Precautions]*.
- Hypersensitivity *[see Warnings and Precautions]*.
- Increased Risk of Adverse Reactions with Abrupt or Rapid Discontinuation *[see Warnings and Precautions]*.

- Suicidal Behavior and Ideation *[see Warnings and Precautions]*.
- Peripheral Edema *[see Warnings and Precautions]*.
- Dizziness and Somnolence *[see Warnings and Precautions]*.
- Weight Gain *[see Warnings and Precautions]*.
- Tumorigenic Potential *[see Warnings and Precautions]*.
- Ophthalmological Effects *[see Warnings and Precautions]*.
- Creatine Kinase Elevations *[see Warnings and Precautions]*.
- Decreased Platelet Count *[see Warnings and Precautions]*.
- PR Interval Prolongation *[see Warnings and Precautions]*.

1-Clinical trials experience

Adverse Reactions Most Commonly Leading to Discontinuation

In the Pregabalin treatment group, the adverse reactions most frequently leading to discontinuation were dizziness and somnolence. Withdrew due to dizziness and somnolence. Other adverse reactions that led to discontinuation more frequently were ataxia, confusion, asthenia, thinking abnormal, blurred vision, incoordination, and peripheral edema.

Most Common Adverse Reactions in all controlled clinical studies in Adults

Adverse Reactions in all adult patient populations combined (including DPN, PHN, and adult patients with partial-onset seizures), dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and "thinking abnormal" (primarily difficulty with concentration/attention).

Controlled studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Adverse Reactions Leading to Discontinuation

In the Pregabalin the most common reasons for discontinuation due to adverse reactions were dizziness and somnolence. Withdrew due to dizziness and somnolence. Other reasons for discontinuation with greater frequency were asthenia, confusion, and peripheral edema. Each of these events led to withdrawal in approximately 1% of patients.

Most Common Adverse Reactions: listed in Table below.

Table 3: Adverse Reaction Incidence in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

Body system	
Body as a whole	Asthenia - Accidental injury - Back pain - Chest pain Face edema.
Digestive system	Dry mouth – Constipation - Flatulence
Metabolic and nutritional disorders	Peripheral edema - Weight gain – Edema - Hypoglycemia
Nervous system	Dizziness – Somnolence – Neuropathy – Ataxia – Vertigo – Confusion – Euphoria – Incoordination – Thinking abnormal- Tremor - Abnormal gait – Amnesia - Nervousness
Respiratory system	Dyspnea
Special senses	Blurry vision - Abnormal vision

Adverse reaction with Postherpetic Neuralgia

Adverse Reactions Leading to Discontinuation

In the Pregabalin treatment group the most adverse reactions were dizziness and somnolence. withdrew due to dizziness and somnolence. Other in greater frequency were confusion, as well as peripheral edema, asthenia, ataxia, and abnormal gait.

Most Common Adverse Reactions

Table 4: Adverse Reaction Incidence in Neuropathic Pain Associated with Postherpetic Neuralgia

Body system	
Body as a whole	Infection – Headache – Pain – Accidental injury - Flu syndrome -Face edema
Digestive system	Dry mouth – Constipation – Flatulence - Vomiting
Metabolic and nutritional disorders	Peripheral edema - Weight gain -Edema
Musculoskeletal system	Myasthenia
Nervous system	Dizziness – Somnolence – Ataxia - Abnormal gait - Confusion - Thinking abnormal- Incoordination – Amnesia - Speech disorder
Respiratory system	Bronchitis
Special senses	Blurry vision – Diplopia – Abnormal vision - Eye Disorder
Urogenital System	Urinary Incontinence

Adverse reaction with Adjunctive Therapy for Partial-Onset Seizures in Adult Patients

Adverse Reactions Leading to Discontinuation

In the Pregabalin treatment group the adverse reactions most frequently were dizziness, ataxia, and somnolence. withdrew due to each of these events. Other adverse reactions were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal patients).

Most Common Adverse Reactions

Table 5: Dose-related Adverse Reaction Incidence in Adjunctive Therapy for Partial-Onset Seizures in Adult Patients

Body System	
Body as a Whole	Accidental Injury - Pain
Digestive System	Increased Appetite - Dry Mouth - Constipation
Metabolic and Nutritional Disorders	Weight Gain -Peripheral Edema
Nervous System	Dizziness – Somnolence – Ataxia – Tremor - Thinking Abnormal – Amnesia - Speech Disorder - Incoordination - Abnormal Gait – Twitching – Confusion - Myoclonus
Special Senses	Blurred Vision – Diplopia - Abnormal Vision

Controlled study of Adjunctive Therapy for Partial-Onset Seizures in Patients 4 to Less Than 17 Years of Age

Adverse Reactions Leading to Discontinuation

In the Pregabalin the adverse reactions leading to discontinuation were somnolence, worsening of epilepsy, and hallucination.

Most Common Adverse Reactions

Table 6: Dose-related Adverse Reaction Incidence in Adjunctive Therapy for Partial-Onset Seizures in Patients 4 to Less Than 17 Years of Age

Body System	
Gastrointestinal disorders	Salivary hypersecretion
Investigations	Weight increased
Metabolism and nutrition disorders	Increased appetite
Nervous system disorders	Somnolence

Controlled study of Adjunctive Therapy for Partial-Onset Seizures in Patients 1 Month to Less Than 4 Years of Age

Most Common Adverse Reactions

Table 7: Dose-related Adverse Reaction Incidence in Adjunctive Therapy for Partial-Onset Seizures in Patients 1 Month to Less Than 4 Years of Age

Body System	
Nervous system disorders	Somnolence
Infections and infestations	Pneumonia - Viral infection

Controlled Studies with Fibromyalgia

Adverse Reactions Leading to Discontinuation

In the Pregabalin the most common adverse reactions were dizziness and somnolence, Withdrew due to dizziness and somnolence.

Other Adverse Reactions occurring with greater frequency were fatigue, headache, balance disorder, and weight increased. Each of these adverse reactions led to withdrawal.

Most Common Adverse Reactions

Table 8. Adverse Reaction Incidence in Controlled Trials Fibromyalgia

System Organ class	
Ear and Labyrinth Disorders	Vertigo
Eye Disorders	Vision blurred
Gastrointestinal Disorders	Dry mouth – Constipation – Vomiting – Flatulence - Abdominal distension
General Disorders and Administrative Site Conditions	Fatigue – Edema peripheral - Chest pain – Feeling abnormal – Edema - Feeling drunk
Infections and Infestations	Sinusitis
Investigations	Weight increased
Metabolism and Nutrition Disorders	Increased appetite - Fluid retention
Musculoskeletal and Connective Tissue Disorders	Arthralgia - Muscle spasms - Back pain
Nervous System Disorders	Dizziness – Somnolence – Headache - Disturbance in attention – Balance disorder – Memory impairment - Coordination abnormal – Hypoesthesia – Lethargy – Tremor
Psychiatric Disorders	Euphoric Mood – Confusional state – Anxiety – Disorientation - Depression
Respiratory, Thoracic and Mediastinal Disorders	Pharyngolaryngeal pain

Controlled Studies in Neuropathic Pain Associated with Spinal Cord Injury

Adverse Reactions Leading to Discontinuation

In pregabalin treatment group the most common adverse reactions were somnolence and edema, withdrew due to somnolence and edema. Other Adverse Reactions occurring with greater frequency were fatigue and balance disorder.

Most Common Adverse Reactions

Table 9. Adverse Reaction Incidence in Neuropathic Pain Associated with Spinal Cord Injury

System Organ class	
Ear and labyrinth disorders	Vertigo
Eye disorders	Vision blurred
Gastrointestinal disorders	Dry mouth – Constipation – Nausea - Vomiting
General disorders and administration site conditions	Fatigue - Edema peripheral – Edema - Pain
Infections and infestations	Nasopharyngitis
Investigations	Weight increased - Blood creatine phosphokinase increased
Musculoskeletal and connective tissue disorders	Muscular weakness - Pain in extremity - Neck pain – Back pain - Joint swelling
Nervous system disorders	Somnolence – Dizziness - Disturbance in attention – Memory impairment - Paresthesia
Psychiatric disorders	Insomnia - Euphoric mood
Renal and urinary disorders	Urinary incontinence
Skin and subcutaneous tissue disorders	Decubitus ulcer
Vascular disorders	Hypertension - Hypotension

Other Adverse Reactions Observed During the Clinical Studies of Pregabalin

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the Warnings and Precautions section.

Body as a Whole

- *Frequent:* Abdominal pain, Allergic reaction, Fever
- *Infrequent:* Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction.
- *Rare:* Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional Injury, Retroperitoneal Fibrosis, Shock.

Cardiovascular System

- *Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope.
- *Rare:* ST Depressed, Ventricular Fibrillation.

Digestive System

- *Frequent*: Gastroenteritis, Increased appetite.
- *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema.
- *Rare*: Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess.

Hemic and Lymphatic System

- *Frequent:* Ecchymosis; Infrequent: Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia.
- *Rare*: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia, Alanine aminotransferase increased, Aspartate aminotransferase increased.

Metabolic and Nutritional Disorders:

- *Rare*: Glucose Tolerance Decreased, Urate Crystalluria.

Musculoskeletal System

- *Frequent:* Arthralgia, Leg cramps, Myalgia, Myasthenia.
- *Infrequent:* Arthrosis.
- *Rare:* Chondrodystrophy, Generalized Spasm.

Nervous System

- *Frequent:* Anxiety, Depersonalization, Hypertonia, Hypoesthesia, Libido decreased, Nystagmus, Paresthesia, Sedation, Stupor, Twitching.
- *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia.
- *Rare*: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus.

Respiratory System

Rare: Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn.

Skin and Appendages

- *Frequent:* Pruritus.
- *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash.
- *Rare:* 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.

Special senses

- *Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus.
- *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion.
- *Rare:*Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis.

Urogenital System

- *Frequent:* Anorgasmia, Impotence, Urinary frequency, Urinary incontinence.
- *Infrequent:* Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality.
- *Rare:* Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis.

2-Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Pregabalin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders – Headache

Gastrointestinal Disorders – Nausea, Diarrhea

Reproductive System and Breast Disorders – Gynecomastia, Breast Enlargement

In addition, there are postmarketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when Averopreg was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. There are also postmarketing reports of respiratory failure and coma in patients taking pregabalin and other CNS depressant medications.

DRUG INTERACTIONS

Since 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. *In vitro* and *in vivo* studies showed that Averopreg 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 Pregabalin and commonly used antiepileptic drugs *[see Clinical Pharmacology]*.

Pharmacodynamics

Multiple oral doses of Pregabalin 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 Pregabalin was co-administered with these drugs. No clinically important effects on respiration were seen.

USE IN SPECIFIC POPULATIONS

1- Pregnancy

The background risk of major birth defects and miscarriage for the indicated populations are unknown. Advise pregnant women of potential risk to a fetus.

2- Lactation

Small amounts of pregabalin have been detected in the milk of lactating women. A pharmacokinetic study in lactating women detected pregabalin in breast milk at average steady state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150 mL/kg/day) was 0.31

mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose. The study did not evaluate the effects of Pregabalin on milk production or the effects of Pregabalin on the breastfed infant.

Based on animal studies, there is a potential risk of tumorigenicity with pregabalin exposure via breast milk to the breastfed infant. Available clinical study data in patients greater than 12 years of age do not provide a clear conclusion about the potential risk of tumorigenicity with pregabalin *[see Warnings and Precautions]*. Because of the potential risk of tumorigenicity, breastfeeding is not recommended during treatment with Pregabalin.

3- Pediatric Use

Neuropathic Pain Associated with Diabetic Peripheral Neuropathy, Postherpetic Neuralgia, and Neuropathic Pain Associated with Spinal Cord Injury

Safety and effectiveness in pediatric patients have not been established.

Fibromyalgia

Safety and effectiveness in pediatric patients have not been established.

The most frequently observed adverse reactions in the clinical trial included dizziness, nausea, headache, weight increased, and fatigue.

Adjunctive Therapy for Partial-Onset Seizures

Safety and effectiveness in pediatric patients below the age of 1 month have not been established.

4 to Less Than 17 Years of Age with Partial-Onset Seizures

The most common adverse reactions (≥5%) with pregabalin in this study were somnolence, weight increased, and increased appetite *[see Adverse Reactions]*.

The use of pregabalin 2.5 mg/kg/day in pediatric patients is further supported by evidence from adequate and well-controlled studies in adults with partial-onset seizures and pharmacokinetic data from adult and pediatric patients *[see Clinical Pharmacology]*.

1 Month to Less than 4 Years of Age with Partial-Onset Seizures

The most common dose-related adverse reactions (≥5%) with pregabalin in this study were somnolence, pneumonia, and viral infection *[see Adverse Reactions]*.

4- Geriatric Use

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

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.

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 *[see Dosage and Administration]*.

5- Renal Impairment

Pregabalin is eliminated primarily by renal excretion and dose adjustment is recommended for adult patients with renal impairment *[see Dosage and Administration and Clinical Pharmacology]*. The use of Pregabalin in pediatric patients with compromised renal function has not been studied.

DRUG ABUSE AND DEPENDENCE

1- Controlled Substance

Pregabalin is a Schedule V controlled substance.

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 Averopreg misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

2- Abuse

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, Averopreg (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4 % of Pregabalin -treated patients and 1 % of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%.

3- Dependence

In clinical studies, following abrupt or rapid discontinuation of Pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea *[see Warnings and Precautions]*, consistent with physical dependence. In the postmarketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

There is limited experience with overdose of Averopreg. The highest reported accidental overdose of Averopreg 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 Averopreg. 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. Contact a Certified Poison Control Center for up-to-date information on the management of overdose with Pregabalin.

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).

CLINICAL PHARMACOLOGY

1- Mechanism of Action

Averopreg (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 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. 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 gamma - aminobutyric acid (GABA), it does not bind directly to $GABA_A$, $GABA_B$, or benzodiazepine receptors, does not augment $GABA_A$ 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.

2- 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 Pregabalin capsules under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is greater than or equal to 90% and is independent of dose. Following single- (25 to 300 mg) and multiple-dose (75 to 900 mg/day) administration, maximum plasma concentrations (C_{max}) 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 C_{max} of approximately 25% to 30% and an increase in T_{max} 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) *[see Dosage and Administration]*.

Pharmacokinetics in Specific Populations

Race

In population pharmacokinetic analyses of the clinical studies in various populations, the pharmacokinetics of Averopreg 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 Averopreg 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 *[see Dosage and Administration]*.

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 *[see Dosage and Administration]*.

Pediatric Pharmacokinetics

Pediatric Patients (3 months to less than 17 years of age)

Pregabalin pharmacokinetics were evaluated in patients less than 17 years of age with partial-onset seizures at dose levels of 2.5, 5, 10, and 15 mg/kg/day after single and multiple oral administration of pregabalin. Following oral administration, pregabalin reaches peak plasma concentration at 0.5 hours to 2 hours in the fasted state. Both apparent clearance (CL/F) and apparent volume of distribution increase as body weight increases.

A weight-based dosing regimen is necessary to achieve pregabalin exposures in pediatric patients 1 month to less than 17 years of age similar to those observed in adults treated for partial-onset seizures at effective doses *[see Dosage and Administration]*. The mean $t_{½}$ is 3 to 4 hours in pediatric subjects up to 6 years of age, and 4 to 6 hours in those 7 years of age and older. Pregabalin CL/F is nearly proportional to CLcr (mL/min). The relationship is similar in pediatric and adult subjects. When normalized per body weight, CL/F (mL/min/kg) in pediatric subjects weighing less than 30 kg is approximately 40% higher in comparison to subjects weighing greater than or equal to 30 kg *[see Dosage and Administration]*.

Drug Interactions

In Vitro Studies

Pregabalin, at concentrations that were, in general, 10-times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. In vitro drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A4 activity. Therefore, an increase in the metabolism of coadministered CYP1A2 substrates (e.g. theophylline, caffeine) or CYP 3A4 substrates (e.g., midazolam, testosterone) is not anticipated.

In Vivo Studies

The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin

The pharmacokinetic interactions of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single-dose administration of 100-mg pregabalin and 300-mg gabapentin and in 18 healthy subjects following concomitant multiple-dose administration of 200-mg pregabalin every 8 hours and 400-mg gabapentin every 8 hours. Gabapentin pharmacokinetics following single- and multiple-dose administration were unaltered by pregabalin coadministration. The extent of pregabalin absorption was unaffected by gabapentin coadministration, although there was a small reduction in rate of absorption.

Oral Contraceptive

Pregabalin coadministration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects.

Lorazepam

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin.

Phenytoin, carbamazepine, valproic acid, and lamotrigine

Steady-state trough plasma concentrations of phenytoin, carbamazepine and carbamazepine 10,11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration.

Population pharmacokinetic analyses in patients treated with pregabalin and various concomitant medications suggest the following:

Therapeutic class	**Specific concomitant drug studied**

Concomitant drug has no effect on the pharmacokinetics of pregabalin	
Hypoglycemic Diuretics	Glyburide, insulin, metformin Furosemide
Antiepileptic Drugs	Tiagabine
Concomitant drug has no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of concomitant drug	
Antiepileptic Drugs	Carbamazepine, lamotrigine, phenobarbital phenytoin, topiramate, valproic acid

Reporting of suspected adverse reactions*:*

Reporting suspected adverse reactions after authorization of the medicinal product is Important. It allows continued monitoring of the benefit/risk balance of the medicinal Product. Healthcare professionals are asked to report any suspected adverse reactions via:

E-mail:

avs@averroespharma.net

regi@averroes-eg.com

Or on the following address:

Block No 6048, 6th industrial zone Sadat city, Egypt. Tel: 0482630201/2, Fax: 0482630203

55 Hafez badawy street Nasr city, Egypt.

Also you can report via:

Egyptian Pharmaceutical Vigilance Center (EPVC)

21 Abd El Aziz Al Soud Street. El-Manial, Cairo, Egypt.

E-mail: pv.center@eda.mohp.gov.eg

Fax Number: +2 02 23684194

Telephone: +2 02 (23648046, 23640368, 23684381, 23684288), Extension No. 1303

HOW SUPPLIED/STORAGE AND HANDLING

1- Nature and contents of container

- Averopreg 50 mg Hard Gelatin Capsule: carton box contains 1 or 2 or 3 strips (Al/white opaque PVC) each of 10 capsules and insert leaflet.
- Averopreg 100 mg Hard Gelatin Capsule: carton box contains1 or 2 or 3 strips (Al/ white opaque PVC) each of 5 capsules and insert leaflet
- Averopreg 100 mg / 5 ml Oral Solution: carton box contains 80 ml HDPE plastic bottle contain 60 ml solution + plastic measure and insert leaflet.

2- Storage conditions

- Averopreg 50 hard gelatin capsule & Averopreg 100 mg hard gelatin capsule

  Store at temperature not exceeding 30 °C in dry place.

- Averopreg 100 mg / 5ml Oral Solution

  Store at temperature not exceeding 30 °C .

3-List of excipients

- Averopreg 50 mg Hard Gelatin Capsule: Lactose monohydrate – maize starch – purified talc – gelatin – titanium dioxide – sunset yellow – Quinoline yellow – Methyl paraben – Propyl paraben – Sodium lauryl sulfate – Aerosil - Brilliant blue and Erythrosine red.
- Averopreg 100 mg Hard Gelatin Capsule: Lactose monohydrate – maize starch – purified talc – gelatin – titanium dioxide –Methyl paraben – Propyl paraben – Sodium lauryl sulfate – Aerosil - Quinoline yellow and Ponceau red.
- Averopreg 100 mg / 5 ml Oral Solution contains : Anhydrous tribasic sodium phosphate – Anhydrous sodium dihydrogen phosphate – Sodium metabisulfite – Sodium edetate – Sucralose – Glycerin –Sorbitol solution 70 % - Cherry flavor liquid and Banana flavor Liquid – purified water.

PATIENT COUNSELING INFORMATION

Angioedema

Advise patients that Averopreg may cause angioedema, with swelling of the face, mouth (lip, gum, tongue) and neck (larynx and pharynx) that can lead to life-threatening respiratory compromise. Instruct patients to discontinue AVEROPREG and immediately seek medical care if they experience these symptoms *[see Warnings and Precautions]*.

Hypersensitivity

Advise patients that Averopreg has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Instruct patients to discontinue Averopreg and immediately seek medical care if they experience these symptoms *[see Warnings and Precautions]*.

Adverse Reactions with Abrupt or Rapid Discontinuation

Advise patients to take Averopreg as prescribed. Abrupt or rapid discontinuation may result in increased seizure frequency in patients with seizure disorders, and insomnia, nausea, headache, anxiety, hyperhidrosis, or diarrhea *[see Warnings and Precautions]*.

Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including Averopreg, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of 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 *[see Warnings and Precautions]*.

Dizziness and Somnolence

Counsel patients that Averopreg may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, advise patients not to drive, operate complex machinery, or engage in other hazardous activities until they have gained sufficient experience on Averopreg to gauge whether or not it affects their mental, visual, and/or motor performance adversely *[see Warnings and Precautions]*.

Weight Gain and Edema

Counsel patients that Averopreg may cause edema and weight gain. Advise patients that concomitant treatment with Averopreg and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure *[see Warnings and Precautions]*.

Ophthalmological Effects

Counsel patients that Averopreg may cause visual disturbances. Inform patients that if changes in vision occur, they should notify their physician *[see Warnings and Precautions]*.

Creatine Kinase Elevations

Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever *[see Warnings and Precautions]*.

CNS Depressants

Inform patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines that they may experience additive CNS side effects, such as somnolence *[see Warnings and Precautions and Drug Interactions]*.

Alcohol

Tell patients to avoid consuming alcohol while taking Averopreg, as Averopreg may potentiate the impairment of motor skills and sedating effects of alcohol.

Missed Dose

Counsel patients if they miss a dose, they should take it as soon as they remember. If it is almost time for the next dose, they should skip the missed dose and take the next dose at their regularly scheduled time. Instruct patients not to take two doses at the same time.

Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to AVEROPREG during pregnancy *[see Use in Specific Populations]*.

Lactation

Advise nursing mothers that breastfeeding is not recommended during treatment with AVEROPREG *[see Use in Specific Populations]*.

Male Fertility

Inform men being treated with AVEROPREG who plan to father a child of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associated with an

increased risk of male-mediated teratogenicity. The clinical significance of this finding is uncertain *[see Nonclinical Toxicology)*

and Use in Specific populations].

Dermatopathy

Instruct diabetic patients to pay particular attention to skin integrity while being treated with AVEROPREG and to inform their healthcare provider about any sores or skin problems. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with AVEROPREG was observed in clinical trials.

Produced by Averroes Pharma for pharmaceutical industries

Block No. 6048 6th industrial zone, Sadat city, Egypt.