PREGY®
(Pregabalin)

1. NAME OF THE PRODUCT

PREGY® (Pregabalin) 25mg Capsule
PREGY® (Pregabalin) 50mg Capsule
PREGY® (Pregabalin) 75mg Capsule
PREGY® (Pregabalin) 100mg Capsule
PREGY® (Pregabalin) 150mg Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PREGY® 25mg Capsule
Each capsule contains:
Pregabalin USP.....25mg

PREGY® 50mg Capsule
Each capsule contains:
Pregabalin USP….50mg

PREGY® 75mg Capsule
Each capsule contains:
Pregabalin USP…..75mg

PREGY® 100mg Capsule
Each capsule contains:
Pregabalin USP…..100mg

PREGY® 150mg Capsule
Each capsule contains:
Pregabalin USP.....150mg

3. PHARMACEUTICAL FORM

Capsule

Appearance:
PREGY® 25mg Capsule: White to almost white crystalline powder in hard gelatin capsules having light green opaque cap printed "**PREGY®** 25mg" and white opaque body with "" printed on it three times.
PREGY® 50mg Capsule: White to almost white crystalline powder in hard gelatin capsules having light blue opaque cap printed "**PREGY®** 50mg" and white opaque body with "" printed on it three times.

PREGY® 75mg Capsule: White to almost white crystalline powder in hard gelatin capsules having green opaque cap printed "**PREGY®** 75mg" and white opaque body with "" printed on it three times.

PREGY® 100mg Capsule: White to almost white crystalline powder in hard gelatin capsule having sea green opaque cap printed "**PREGY®** 100mg" and sea green opaque body with "" printed on it three times.

PREGY® 150mg Capsule: White to almost white crystalline powder in hard gelatin capsules having blue opaque cap printed "**PREGY®** 150mg" and blue opaque body with "" printed on it three times.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

PREGY® 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

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Neuropathic pain associated with diabetic peripheral neuropathy in adults: The maximum recommended dose of **PREGY®** is 100mg three times a day (300mg/day) in patients with creatinine clearance of at least 60mL/min. Begin dosing at 50mg three times a day (150mg/day). The dose may be increased to 300mg/day within 1 week based on efficacy and tolerability. Although **PREGY®** was also studied at 600mg/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 300mg/day is not recommended.

Postherpetic neuralgia in adults: The recommended dose of **PREGY®** is 75 to 150mg two times a day, or 50 to 100mg three times a day (150 to 300mg/day) in patients with creatinine clearance of at least 60mL/min. Begin dosing at 75mg two times a day, or 50mg three times a day (150mg/day). The dose may be increased to 300mg/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 300mg/day, and who are able to tolerate **PREGY®**, may be treated with up to 300mg two times a day, or 200mg three times a day (600mg/day). In view of the dose-dependent adverse reactions and the higher

rate of treatment discontinuation due to adverse reactions, reserve dosing above 300mg/day for those patients who have on-going pain and are tolerating 300mg daily.

Adjunctive therapy for partial-onset seizures in patients 1 month of age and older: The recommended dosages for adults and paediatric patients 1 month of age and older are included in Table. Administer the total daily dosage orally in two or three divided doses as indicated in Table. 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 month and older:

Age and Body Weight	Recommended Initial Dosage	Recommended Maximum Dosage	Frequency of Administration
Adults (17 years and older)	150mg/day	600mg/day	2 or 3 divided doses
Paediatric patients weighing 30kg or more	2.5mg/kg/day	10mg/kg/day (not to exceed 600mg/day)	2 or 3 divided doses
Paediatric patients weighing less than 30kg	3.5mg/kg/day	14mg/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

Management of fibromyalgia in adults: The recommended dose of **PREGY®** for fibromyalgia is 300 to 450mg/day. Begin dosing at 75mg two times a day (150mg/day). The dose may be increased to 150mg two times a day (300mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300mg/day may be further increased to 225mg two times a day (450mg/day). Although **PREGY®** was also studied at 600mg/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 450mg/day is not recommended.

Neuropathic pain associated with spinal cord Injury in adults: The recommended dose range of **PREGY®** for the treatment of neuropathic pain associated with spinal cord injury is 150 to 600mg/day. The recommended starting dose is 75mg two times a day (150mg/day). The dose may be increased to 150mg two times a day (300mg/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 150mg two times a day and who tolerate **PREGY®** may be treated with up to 300mg two times a day.

Dosing for adult patients with renal Impairment: In view of dose-dependent adverse reactions and since **PREGY®** is eliminated primarily by renal excretion, adjust the dose in adult patients with reduced renal function. The use of **PREGY®** in paediatric 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. 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:

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

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 60mL/min).

(For example: A patient initiating **PREGY®** therapy for postherpetic neuralgia with normal renal function (CLcr greater than or equal to 60mL/min), receives a total daily dose of 150mg/day pregabalin. Therefore, a renal impaired patient with a CLcr of 50mL/min would receive a total daily dose of 75mg/day pregabalin administered in two or three divided doses.)

For patients undergoing haemodialysis, 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 haemodialysis treatment.

Pregabalin dose 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
15	25	25-50	50-75	75	QD

Supplementary dosage following haemodialysis (mg)**
Patients on the 25mg QD regimen: take one supplemental dose of 25mg or 50mg Patients on the 25–50mg QD regimen: take one supplemental dose of 50mg or 75mg Patients on the 50–75mg QD regimen: take one supplemental dose of 75mg or 100mg Patients on the 75mg QD regimen: take one supplemental dose of 100mg or 150mg

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

Paediatric Use:
Neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and neuropathic pain associated with spinal cord Injury: Safety and effectiveness in paediatric patients have not been established.
Fibromyalgia: Safety and effectiveness in paediatric patients have not been established.
Adjunctive therapy for partial-onset seizures: Safety and effectiveness in paediatric patients below the age of 1 month have not been established.
4 to less than 17 years of age with partial-onset seizures: The safety and effectiveness of **PREGY®** as adjunctive treatment for partial-onset seizures in pediatric patients 4 to less than 17 years of age have been established. The most common adverse reactions (≥5%) with **PREGY®** in this study were somnolence, weight increased, and increased appetite.
1 month to less than 4 years of age with partial-onset seizures: The safety and effectiveness of **PREGY®** as adjunctive treatment for partial-onset seizures in paediatric patients 1 month to less than 4 years of age have been established. The most common dose-related adverse reactions (≥5%) with **PREGY®** in this study were somnolence, pneumonia, and viral infection.
Elderly use: No overall differences in safety and efficacy were observed between elderly patients and younger patients. 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.
Renal Impairment: PREGY® is eliminated primarily by renal excretion and dose adjustment is recommended for adult patients with renal impairment. The use of **PREGY®** in paediatric patients with compromised renal function has not been studied.

Method of administration:
PREGY® is given orally with or without food.
When discontinuing **PREGY®**, taper gradually over a minimum of 1 week.

4.3. CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients.
Angioedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Angioedema: There have been post-marketing 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.
Hypersensitivity: There have been post-marketing reports of hypersensitivity in patients shortly after initiation of treatment with Pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnoea, and wheezing. Discontinue Pregabalin immediately in patients with these symptoms.
Suicidal behavior and Ideation: 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 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. The risk of suicidal thoughts or behavior beyond 24 weeks has not been 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.
Respiratory depression: There is evidence from case reports, human studies, and animal studies associating Pregabalin with 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 impairment. 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 patients for symptoms of respiratory depression and sedation, and consider initiating Pregabalin at a low dose. The management of respiratory depression may include close observation, supportive measures, and reduction or withdrawal of CNS depressants (including Pregabalin). There is more limited evidence from case reports, animal studies, and human studies associating Pregabalin with serious respiratory depression, without co-administered CNS depressants or without underlying respiratory impairment.

Dizziness and somnolence: 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.

Increased risk of adverse reactions with abrupt or rapid discontinuation: 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, hyperhidrosis, and diarrhoea. If Pregabalin is discontinued, taper the drug gradually over a minimum of 1 week rather than discontinue the drug abruptly.

Peripheral oedema: Pregabalin treatment may cause peripheral oedema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral oedema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral oedema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. 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.

Weight gain: 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 oedema. Although weight gain was not associated with clinically important changes in blood pressure, the long-term cardiovascular effects of Pregabalin associated weight gain are unknown. Pregabalin treatment did not appear to be associated with loss of glycaemic control (as measured by HbA1c).

Tumorigenic potential: In standard preclinical *in vivo* lifetime carcinogenicity studies of Pregabalin, an unexpectedly high incidence of haemangiosarcoma 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.

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.

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

Decreased Platelet Count: Pregabalin treatment was associated with a decrease in platelet count.

PR Interval Prolongation: Pregabalin treatment was associated with PR interval prolongation.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF 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 Pregabalin 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.

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.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: In the animal fertility study with pregabalin in male rats, adverse reproductive and developmental effects were observed.

Pregnancy: There are no adequate and well-controlled studies with Pregabalin in pregnant women.

Breast-feeding: Small amounts of pregabalin have been detected in the milk of lactating women. Because of the potential risk of tumorigenicity, breast-feeding is not recommended during treatment with Pregabalin.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Pregabalin may cause dizziness, somnolence and impair patients' ability to drive or operate machinery.

4.8. UNDESIRABLE EFFECTS:

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.

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 haemorrhage, melaena, mouth ulceration, pancreatitis, rectal haemorrhage, tongue oedema

Rare: Aphthous stomatitis, esophageal ulcer, periodontal abscess

Haemic and lymphatic system:

Frequent: Ecchymosis

Infrequent: Anaemia, eosinophilia, hypochromic anaemia, leukocytosis, leukopaenia, lymphadenopathy, thrombocytopaenia

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, paraesthesia, sedation, stupor, twitching

Infrequent: Abnormal dreams, agitation, apathy, aphasia, circumoral paraesthesia, 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: Apnoea, atelectasis, bronchiolitis, hiccup, laryngismus, lung oedema, 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 haemorrhage, hyperacusis, photophobia, retinal oedema, 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, haematuria, 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

The following adverse reactions have been identified during post-approval 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.

Additional reactions reported from post-marketing experience are included in the list below.

Nervous system disorders:

Headache

Gastrointestinal disorders:
Nausea, diarrhoea
Reproductive system and breast disorders:
Gynecomastia, breast enlargement
Skin and subcutaneous tissues disorders:
Bullous pemphigoid.
There are post-marketing reports of life-threatening or fatal respiratory depression in patients taking Pregabalin with opioids or other CNS depressants, or in the setting of underlying respiratory impairment. In addition, there are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g., intestinal obstruction, paralytic ileus, constipation) when Pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics.

4.9. OVERDOSE:

Signs, symptoms and laboratory findings of acute overdosage in humans: In the post-marketing experience, the most commonly reported adverse events observed with pregabalin when taken in overdose include reduced consciousness, depression/anxiety, confusional state, agitation, and restlessness. Seizures and heart block have also been reported. Deaths have been reported in the setting of lone Pregabalin overdose and in combination with other CNS depressants.
Treatment or management of overdose: 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 care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. Pregabalin can be removed by haemodialysis. Standard haemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Analgesic, other analgesic and antipyretics.
ATC code: N02BF02.
Mechanism of action: Pregabalin binds with high affinity to the alpha$_2$-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. 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.

5.2. PHARMACOKINETICS PROPERTIES:

Absorption: 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 300mg) and multiple-dose (75 to 900mg/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} 30% and an increase in T_{max} of approximately 25% 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.

Distribution: Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5L/kg. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood brain barrier.

Metabolism: Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled 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.

Elimination: 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 80.9mL/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).

5.3. PRECLINICAL SAFETY DATA:

Carcinogenesis: A dose-dependent increase in the incidence of malignant vascular tumors (haemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased haemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600mg/day. A no-effect dose for induction of haemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450mg/kg in males and 100, 300, or 900mg/kg in females) that were

associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD.

Mutagenesis: Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Impairment of Fertility: In fertility studies in which male rats were orally administered pregabalin (50 to 2500mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased foetal body weights, and an increased incidence of foetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3–4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600mg/day. In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD. In a fertility study in which female rats were given pregabalin (500, 1250, or 2500mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

PREGY® 25mg Capsule:

- Maize Starch
- Talcum Powder
- Lactose Monohydrate
- Hard Gelatin Capsule

PREGY® 50mg Capsule:

- Maize Starch
- Talcum Powder
- Lactose Monohydrate
- Hard Gelatin Capsule

PREGY® 75mg Capsule:

- Maize Starch
- Talcum Powder
- Lactose Monohydrate
- Hard Gelatin Capsule

PREGY® 100mg Capsule:

- Maize Starch
- Talcum Powder
- Lactose Monohydrate
- Hard Gelatin Capsule

PREGY® 150mg Capsule:

- Maize Starch
- Talcum Powder
- Lactose Monohydrate
- Hard Gelatin Capsule

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Keep out of reach of children.
Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.

6.5. NATURE AND CONTENTS OF CONTAINER:

PREGY® 25mg Capsule: Alu/Alu blister packing, pack size is 14's.
PREGY® 50mg Capsule: Alu/Alu blister packing, pack size is 14's.
PREGY® 75mg Capsule: Alu/Alu blister packing, pack size is 14's.
PREGY® 100mg Capsule: Alu/Alu blister packing, pack size is 14's.
PREGY® 150mg Capsule: Alu/Alu blister packing, pack size is 14's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused product should be disposed of according to local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

PREGY® 25mg Capsule: BP Specs.
PREGY® 50mg Capsule: BP Specs.
PREGY® 75mg Capsule: BP Specs.

PREGY® 100mg Capsule: BP Specs.
PREGY® 150mg Capsule: BP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

PREGY® 25mg Capsule: 076674
PREGY® 50mg Capsule: 076670
PREGY® 75mg Capsule: 076671
PREGY® 100mg Capsule: 076672
PREGY® 150mg Capsule: 076673

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

PREGY® 25mg Capsule: 23rd January, 2015
PREGY® 50mg Capsule: 23rd January, 2015
PREGY® 75mg Capsule: 23rd January, 2015
PREGY® 100mg Capsule: 23rd January, 2015
PREGY® 150mg Capsule: 23rd January, 2015

10. DATE OF REVISION OF THE TEXT

N/A

پریگی® کیپسول

(پریگیبالِن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی۔