For the use only of Registered Medical Practitioner

1. Generic Name and Brand Name

Dosulepin 75 mg, Pregabalin 75 mg, and Mecobalamin 1500 mcg Capsules
PROTHIADEN® NEU

2. Qualitative and Quantitative Composition:

Each Hard Gelatin Capsule Contains:
Pregabalin I.P……75 mg
Dosulepin Hydrochloride I.P……75 mg
Mecobalamin I.P…….1500 mcg
Excipients……..q.s.
Colours: Brilliant Blue FCF, Ponceau 4R, Sunset Yellow FCF & Titanium Dioxide I.P.
Appropriate overages of vitamin added to compensate loss on storage.

3. Dosage Form & strength

Refer section 1 & 2

4. Clinical particulars

4.1 Therapeutic indication

Neuropathic Pain

4.2 Posology and method of administration

Posology
Adults & Elderly: One capsule once a day.

Children: The use of FDC of Dosulepin, Pregabalin and methylcobalamin in children has not been studied.

Method of Administration:
Take the FDC once a day before bedtime, orally.

4.3 Contraindications

Contraindicated for patients with known hypersensitivity to Dosulepin hydrochloride, pregabalin, methylcobalamine or any of the excipients, recent myocardial infarction, any degree of heart block or other cardiac arrhythmias, mania and severe liver disease.

4.4 Special warnings and precautions for use

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. Avoid use in patients with a history of epilepsy, thyroid disease, mania or urinary retention and in those with narrow-angle glaucoma or symptoms suggestive of prostatic hypertrophy. Patients with hepatic impairment, those undergoing electroconvulsive therapy and in patients with suspected cardiovascular disease should also avoid FDC use. Angioedema (e.g., swelling of the throat, head and neck) can occur, and may be associated with life-threatening respiratory compromise

requiring emergency treatment. Discontinue FDC immediately in these cases. Increased seizure frequency or other adverse reactions may occur if FDC is rapidly discontinued. Withdraw FDC gradually over a minimum of 1 week. Antiepileptic drugs, including Pregabalin, increase the risk of suicidal thoughts or behavior. may cause peripheral edema. Exercise caution when co administering FDC containing pregabalin and thiazolidinedione antidiabetic agents.
Reduce the dose in patients with impaired renal function and with impaired hepatic function.

4.5 Drug Interactions

Exercise caution when co administering FDC containing pregabalin and thiazolidinedione antidiabetic agents.

Dosulepin should not be given concurrently with a monoamine oxidase (MAO) inhibitor or within 14 days of ceasing such treatment.

The concomitant administration of Dosulepin and selective serotonin reuptake inhibitors (SSRIs) should be avoided since increases in plasma tricyclic antidepressant levels have been reported following the co-administration of some SSRIs.

Dosulepin may alter the pharmacological effect of some concurrently administered drugs including CNS depressants such as alcohol and narcotic analgesics; the effect of these will be potentiated, as will the effects of adrenaline and noradrenaline.

Anesthetics given during tricyclic/tetracyclic antidepressant therapy may increase the risk of arrhythmias and hypotension.

Dosulepin has quinidine-like actions on the heart. For this reason, its concomitant use with other drugs that may affect cardiac conduction (e.g. sotalol, terfenadine, astemizole, halofantrine) should be avoided.

The hypotensive activity of certain antihypertensive agents (e.g. bethanidine, debrisoquine, guanethidine) may be reduced by Dosulepin. It is advisable to review all antihypertensive therapy during treatment with tricyclic antidepressants.

There is an increased risk of postural hypotension when tricyclic antidepressants are given with diuretics.

Tricyclic antidepressants may also antagonize the anticonvulsant effect of antiepileptics (convulsive threshold decreased).

Barbiturates may decrease and methylphenidate may increase the serum concentration of Dosulepin and thus affect its antidepressant action.

There is no evidence that Dosulepin interferes with standard laboratory tests.

Methylcobalamin: Metformin, H_2 receptor antagonists (Cimetidine, Ranitidine etc), Aminoglycosides, Colchicine, Aminosalicylic Acid, Anticonvulsants and Alcohol decrease absorption of Vitamin B12. Chloramphenicol should not be used with methylcobalamin.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use) Pregnancy: May cause fetal harm. Advise of potential risk to the fetus. Lactation: Breastfeeding is not recommended.
The use of FDC of Dosulepin, Pregabalin and methylcobalamin in pediatric age group has not been studied.

4.7 Effects on ability to drive and use machines
Pregabalin and Dosulepin containing FDC may cause dizziness and somnolence and impair patients' ability to drive or operate machinery.

4.8 Undesirable effects

Most common adverse reactions (greater than or equal to 5% and twice placebo) in adults are dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and thinking abnormal (primarily difficulty with concentration/attention). Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), Severe respiratory depression, Bone marrow depression, agranulocytosis, Hypersensitivity reactions, Inappropriate antidiuretic hormone (ADH) secretion, endocrine side effects, Hyponatremia, Psychotic manifestations, including mania and paranoid delusions, suicidal ideation and suicidal behavior, Tremors, drowsiness, convulsions, movement disorders, dizziness, Dyspepsia, abdominal pain, diarrhea and nausea.

4.9 Overdose
Symptoms of overdosage with Dosulepin:
Deaths may occur from overdosage with this class of drugs. Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. Onset of toxicity occurs within 4-6 hours after tricyclic antidepressant overdose.

Symptoms of overdose include dry mouth, excitement, ataxia, drowsiness, unconsciousness, muscle twitching, convulsions, widely dilated pupils, hyperreflexia, sinus tachycardia, cardiac arrhythmias, hypotension, hypothermia, depression of respiration, visual hallucinations, delirium, urinary retention, paralytic ileus, and respiratory or metabolic alkalosis.

Patients ingesting >5 mg/kg should seek immediate medical attention.

All children ingesting Dosulepin should be assessed by a physician.

Treatment:
A clear airway and adequate ventilation should be ensured. Hypoxia and acid-base imbalances should be corrected by assisted ventilation and intravenous sodium bicarbonate as appropriate.

Do not give flumazenil to reverse benzodiazepine toxicity in mixed overdoses.

The use of activated charcoal should be considered as a preferred initial means of reducing absorption in patients presenting within 2 hours of ingestion. Repeated gastric/intestinal aspiration or repeated administration of activated charcoal may remove drug and metabolites excreted into the gut via the bile.

The benefit of gastric lavage is uncertain and the technique should be avoided in any patient with an impaired airway. When the patient is unconscious, or the cough reflex is depressed, the lungs should be protected by a cuffed endotracheal tube.

Forced diuresis is not recommended.

Blood pressure, pulse and cardiac rhythm should be monitored for at least 6 hours after ingestion.

Arrhythmias are best treated by correcting hypoxia and acid-base disturbances.
Specialist poisons advice should be sought before using any anti-arrhythmic agents as these may exacerbate the arrhythmia. In cases of cardiac arrest, persist with prolonged CPR (for at least 1 hour).

Convulsions should be controlled with intravenous diazepam or lorazepam.

Bed rest is advisable, even after recovery.

Overdose of Pregabalin: The highest reported accidental overdose of Pregabalin 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 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. Contact a Certified Poison Control Center for upto-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).

5. Pharmacological properties

5.1 Mechanism of action

Dosulepin is a TCA (Tricyclic Antidepressant) which relieve pain by blocking the neuronal reuptake of norepinephrine and serotonin, thereby potentiating the inhibitory effect these neurotransmitters have in nociceptive pathways.

Methylcobalamin acts as an important cofactor in the reaction of one class of the B 12 enzymes, the methyltransferases.

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 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.

5.2 Pharmacodynamic Properties

The secondary amine metabolite of Dosulepin is a potent and selective noradrenaline reuptake inhibitor and this metabolite may contribute to the antidepressant effect. The other metabolites, Dosulepin sulphoxide and northiaden sulphoxide, are essentially inactive.

B 12 -dependent methyltransferases play an important role in amino acid metabolism in many organisms as well as in one-carbon metabolism and CO 2 fixation in anaerobic microbes. Among them, methionine synthase is the most extensively studied B 12 -dependent methyltransferase in humans. As the cofactor of the enzyme methionine synthase, methylcobalamin functions to catalyse the transfer of the methyl group from methylenetetrahydrofolate to homocysteine (Hcy) to form methionine and tetrahydrofolate.

In an in vitro study, chronic administration of methylcobalamin protected cultured retinal neurons against NMDA-receptor-mediated glutamate neurotoxicity, probably by altering the membrane properties through SAM-mediated methylation. It was also suggested that altered membrane properties induced by SAM-mediated methylation is the major route of the neuroprotective effect of methylcobalamin in several types of CNS insults.

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.

5.3 Pharmacokinetic properties

Dosulepin:

Dosulepin is readily absorbed from the gastrointestinal tract and extensively metabolized in the liver. Metabolites include northiaden, Dosulepin-S-oxide, and northiaden-S-oxide.

The dose is excreted in the urine, mainly in the form of metabolites; appreciable amounts are also excreted in the feces. A half-life of about 50 hours has been reported for Dosulepin and its metabolites.

Absorption

Following oral administration of single doses of 50 to 150 mg Dosulepin to healthy subjects, peak plasma concentrations of Dosulepin were achieved with 3 to 4 hours.

These concentrations were proportional to the administered does and there were wide inter-subject variation in the concentrations obtained.

In elderly healthy subjects who received a single oral dose of Dosulepin 25 mg peak plasma concentrations, time to peak concentration, and AUC values were all increased in comparison with young healthy subjects.

Distribution

There is a wide variation in the mean apparent volume of distribution of the drug when it has been administered as a single oral dose to healthy subjects, although rapid distribution after single 75 mg doses has been reported (distribution half-life 2.6 to 2.9 hours). The volume of distribution is 45L/kg.

The apparent volume of distribution was found to be more variable that the elimination half-life of Dosulepin and could account for the wide range of steady state concentrations which have been found in patients taking Dosulepin.

Dosulepin is 84% protein bound.

Biotransformation

Dosulepin undergoes extensive metabolism by hepatic microsomal enzyme after absorption for the gastrointestinal tract. The main metabolic pathways in humans are S-oxidation and N-demethylation, resulting in the formation of the metabolites Dosulepin-S-oxide, northiaden (desmethyl Dosulepin), and northiaden-S-oxide, which may become conjugated with glucuronic acid.

It has been estimated that the oral bioavailability of Dosulepin is about 30% after first-pass hepatic metabolism, assuming there is complete absorption.

Elimination

Following administration of single oral doses of Dosulepin 50 to 150 mg to healthy subjects, the terminal elimination half-lives of the parent drug and its metabolites were as follows :

Dosulepin	18.5 – 21.5 hours
Dosulepin-S-oxide	22.7 – 25.5 hours
Northiaden	37.6 – 45.7 hours
Northiaden-S-oxide	26.7 – 33.4 hours

The major route of elimination is the kidney. After 96 hours, 56% of the administered dose was recovered from the urine and 15% from the feces.

Methylcobalamin:

Evidence indicates that mecobalamin is used somewhat more efficiently than cyanocobalamin in increasing the levels of one of the coenzyme forms of vitamin B 12. Experiments have demonstrated similar absorption of mecobalamin following oral administration. The quantity of cobalamin detected following a small oral dose of methylcobalamin is similar to the amount detected following the administration of cyanocobalamin, but significantly more cobalamin accumulates in liver tissue, which is associated with mecobalamin intake. Cobalamin circulates in plasma bound to two carrier proteins: transcobalamin (TC) and haptocorrin. TC is a 43-kDa non-glycoprotein that transfers cobalamin from the intestine into the blood stream and then into all the cells of the body. Cobalamin-saturated transcobalamin (holoTC) constitutes 6 – 20% of total plasma cobalamin. The unsaturated TC is called apotranscobalamin, which constitutes the major part of TC. Additionally, total homocysteine (tHcy) and methylmalonic acid are considered to be two functional markers of vitamin B 12 status in adults.

Pregabalin: 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 (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 (Senantiomer) 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)**.**

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Dosulepin is present in low concentrations in breast milk. It crosses the placental and blood-brain barriers in animals. Animal studies in the dog and cat show maximal concentration after 24 hours in liver, uveal tract of the eye, lung, kidney, pituitary and thyroid in descending order. In dogs, the tissue/plasma ratio for uveal tract tissue was 257:1.There is active enterohepatic circulation in animals but this has not been shown in humans.

Dermatopathy Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. Ocular Lesions Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) greater than or equal to 2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.

7. Description

Prothiaden Neu is supplied for oral administration, as Hard Gelatin Capsule of Pregabalin, Dosulepin Hydrochloride and Mecobalamin. Each Hard Gelatin Capsule of Prothiaden Neu contains Pregabalin 75 mg, Dosulepin Hydrochloride 75 mg and Mecobalamin 1500 mcg.

8. Pharmaceutical particulars

8.1 Incompatibilities

NA

8.2 Shelf Life

Refer Pack

8.3 Packaging Information

Refer Pack

8.4 Storage condition & handling instructions

Refer Pack

9. Patient Counseling Information

Angioedema Advise patients that PREGABALIN 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 PREGABALIN and immediately seek medical care if they experience these symptoms.

Hypersensitivity Advise patients that PREGABALIN has been associated with hypersensitivity reactions such as wheezing, dyspnea, rash, hives, and blisters. Instruct patients to discontinue PREGABALIN and immediately seek medical care if they experience these symptoms.
Adverse Reactions with Abrupt or Rapid Discontinuation Advise patients to take PREGABALIN 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.
Suicidal Thinking and Behavior Patients, their caregivers, and families should be counseled that AEDs, including PREGABALIN, 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.

Dizziness and Somnolence Counsel patients that PREGABALIN 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 PREGABALIN to gauge whether or not it affects their mental, visual, and/or motor performance adversely.

Weight Gain and Edema Counsel patients that PREGABALIN may cause edema and weight gain. Advise patients that concomitant treatment with PREGABALIN 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.

Ophthalmological Effects Counsel patients that PREGABALIN may cause visual disturbances. Inform patients that if changes in vision occur, they should notify their physician.
Creatine Kinase Elevations Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever.

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.

Alcohol Tell patients to avoid consuming alcohol while taking PREGABALIN, as PREGABALIN 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 PREGABALIN during pregnancy.

Lactation Advise nursing mothers that breastfeeding is not recommended during treatment with PREGABALIN.

Male Fertility Inform men being treated with PREGABALIN who plan to father a child of the potential risk of malemediated 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.

Dermatopathy Instruct diabetic patients to pay particular attention to skin integrity while being treated with PREGABALIN 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 PREGABALIN was observed in clinical trials.

Dosulepin is an antidepressant medicine. It's used to treat depression. Dosulepin is available on prescription. Most adults (aged over 18 years) can take dosulepin. But dosulepin isn't suitable, or the best option, for some people.

Check with your doctor if you: have had an allergic reaction to dosulepin or any other medicine in the past have a heart problem – dosulepin can make some heart problems worse have a rare illness called porphyria have liver or kidney problems have epilepsy or are having electroconvulsive treatment – dosulepin may increase your risk of having a seizure have an eye problem called glaucoma – dosulepin can increase the pressure in your eye have thoughts about harming yourself or ending your life are trying to become pregnant, are already pregnant or are breastfeeding.

It's usual to take dosulepin once a day before bedtime. This is because it can make you feel sleepy. If you're still feeling drowsy the next day, try taking it earlier in the evening. Dosulepin doesn't usually upset your stomach, so you can take it with or without food. Swallow the capsule whole with a drink of water. Do not chew it, as it tastes bitter.

If you take dosulepin once a day and forget a dose, take your next dose the next day at the usual time. If you take dosulepin 2 or 3 times a day and forget a dose, take it as soon as you remember unless it's nearly time for your next dose. Never take 2 doses at the same time to make up for a forgotten one. Some of the common side effects like dry mouth, constipation, etc. gradually improve as your body gets used to dosulepin. Serious side effects happens rarely, but some people have serious side effects after taking dosulepin. In particular, there's an increased risk of heart problems. Tell your doctor if you are trying to get pregnant, are pregnant, breastfeeding. Make sure your doctor and pharmacist know what other medicines you are taking. This is important when you start or stop any other medicines, or when you have the dose changed.

10. Details of manufacturer
Refer Pack for manufacturer details.

11. Details of permission or licence number
Refer Pack for Permission/License details.

12. Date of revision
Version 2.0, dated 20/12/2024

Version No.2.0, dated 20th December 2024
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