PREGEB MNT

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only
abbreviated prescribing information for PREGEB MNT (Pregabalin (Prolonged Release), Methylcobalamin and Nortriptyline Hydrochloride Tablets) [Please refer the complete prescribing information available at www.torrentpharma.com]

PHARMACOLOGICAL PROPERTIES: **Nortriptyline HCl**: The mechanism of mood elevation by tricyclic antidepressants is at present unknown. Nortriptyline HCl is not a monoamine oxidase inhibitor. It inhibits the activity of such diverse agents as histamine, 5-hydroxytryptamine, and acetylcholine. It increases the pressor effect of norepinephrine but blocks the pressor response of phenethylamine. Studies suggest that nortriptyline HCl interferes with the transport, release, and storage of catecholamines. Operant conditioning techniques in rats and pigeons suggest that nortriptyline HCL has a combination of stimulant and depressant properties. **Pregabalin*:*** it binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system. **Mecobalamin*:*** It is a Neurotropic and acts as a growth promoter for nerve cells, a property which helps to regenerate Central and Peripheral nervous tissue damaged in disorder such as diabetic peripheral neuropathy.

INDICATION: PREGEB MNT tablets are indicated for the treatment of patients with diabetic peripheral neuropathic pain with coexistent vitamin B12 deficiency.

DOSAGE AND ADMINISTRATION: Film coated bilayered tablet, to be taken orally.

CONTRAINDICATION: Known hypersensitivity to any of the active constituents

WARNINGS & PRECAUTIONS: **Nortriptyline*:*** Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. **Pregabalin:** *Diabetic patients:* In accordance with reported current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products. *Hypersensitivity reactions:* There have been reports in the post-marketing experience of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur. *Dizziness, somnolence, loss of consciousness, confusion, and mental impairment:* Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product. *Vision-related effects:* In reported controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients. In the post-marketing experience, visual adverse reactions

have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

DRUG INTERACTIONS: Mecobalamin: None supplied. **Pregabalin:** Since pregabalin is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (< 2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions. ***In vivo reported studies and population pharmacokinetic analysis:*** Accordingly, in reported in vivo studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic analysis indicated that oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance. ***Oral contraceptives, norethisterone and/or ethinyloestradiol*:** Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyloestradiol does not influence the steady-state pharmacokinetics of either substance. ***Central nervous system influencing medical products*:** Pregabalin may potentiate the effects of ethanol and lorazepam. In reported controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. ***Interactions and the elderly*:** No specific pharmacodynamic interaction reported studies were conducted in elderly volunteers. Interaction studies have only been performed in adults. **Nortriptyline HCL:** Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Close supervision and careful adjustment of the dosage are required when nortriptyline HCl is used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine and tricyclic antidepressants can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. The patient should be informed that the response to alcohol may be exaggerated. A case of significant hypoglycemia has been reported in a type II diabetic patient maintained on chlorpropamide (250 mg/day), after the addition of nortriptyline (125 mg/day).

ADVERSE REACTIONS: Mecobalamin: *Anaphylactoid reaction:* Anaphylactoid reaction such as decrease in blood pressure or dyspnea, may occur. Patients should be carefully observed. In the event of such symptoms, treatment should be discontinued immediately and appropriate measures taken. **Pregabalin:** The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence. **Nortriptyline:** *Blood and lymphatic system disorders*: Bone-marrow depression, including agranulocytosis; aplastic anaemia; eosinophilia; purpura; thrombocytopenia. *Immune system disorders*: Petechiae, itching, photosensitisation (avoid excessive exposure to sunlight), drug fever, cross-sensitivity with other tricyclic drugs. *Endocrine disorders*: Syndrome of inappropriate secretion of antidiuretic hormone. *Psychiatric disorders:* Delusions, drowsiness, nightmares, hypomania, exacerbation of psychosis, impotence. Cases of suicidal ideation and suicidal behaviours have been reported during nortriptyline therapy or early treatment discontinuation. *Nervous system disorders*: Numbness, tingling, tremors, extrapyramidal symptoms; seizures, alteration of EEG patterns, tinnitus. Anticholinergic effects: Rarely associated sublingual adenitis or gingivitis, disturbance of accommodation, paralytic ileus, delayed micturition, dilation of the urinary tract.. *Cardiac disorders*: Palpitation, Myocardial infarction, arrhythmias, heart block, stroke. *Gastrointestinal disorders*: Epigastric distress, peculiar taste, stomatitis, abdominal cramps, black tongue, paralytic ileus, parotid swelling. *Hepatobiliary disorders:* Altered liver function, liver necrosis. *Skin and subcutaneous tissue disorders*: Alopecia. *Renal and urinary disorders:* Nocturia.

Reproductive system disorders: Testicular swelling. *General disorders and administration site conditions:* Sweating; weakness. *Withdrawal symptoms*: Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache and malaise.

MARKETED BY:

TORRENT PHARMACEUTICALS LTD.

IN/ PREGEB MNT/MAY-2022/01/ABPI
(Additional information is available on request)