"To be sold by retail on the prescription of a R.M.P. only"

PREGABA-MNT

1. Generic Name:

Pregabalin (Prolonged Release), Methylcobalamin and Nortriptyline Hydrochloride Tablets

2. Qualitative and quantitative composition:

Each film coated bilayered tablet contains:

Pregabalin I.P. …….75 mg

(Prolonged Release)

Methylcobalamin I.P. ……. 1500 mcg

Nortriptyline Hydrochloride I.P.

Eqv. to Nortriptyline…….10 mg

Excipients…….q.s.

Colour: Sunset Yellow Lake

(In Methylcobalamin and Nortriptyline layer)

The excipients used are Crospovidone, Colloidal Silicon Dioxide, Hydroxy Propyl Cellulose, Starch 1500, Microcrystalline Cellulose, Sodium Stearyl Fumarate, Hydroxy Propyl Methyl Cellulose, Lactose, Isopropyl Alcohol, Colloidal Silicone Dioxide, Methylene Dichloride, Sunset Yellow Lake.

3. Dosage form and strength:

Dosage form: Film coated bilayered tablet

Strength: Pregabalin 75mg (Prolonged Release), Methylcobalamin 1500mcg and Nortriptyline 10mg

4. Clinical particulars:

4.1 Therapeutic indication:

PREGABA-MNT tablets are indicated for the treatment of patients with diabetic peripheral neuropathic pain with coexistent vitamin B12 deficiency.

4.2 Posology and method of administration:

<u>Posology</u>

Once a daily Pregabalin (PR) 75 mg + Nortriptyline Hydrochloride 10 mg + Mecobalamin 1500 mcg film coated bilayered tablet or as directed by the Physician.

Method of administration

To be taken orally

4.3 Contraindications:

Known hypersensitivity to any of the active constituents

4.4 Special warnings and precautions for use:

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.

4.5 Drug-Interaction:

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).

4.6 Use in special populations:

MECOBALAMIN

The usual precautions should be observed when administering drugs during pregnancy, especially in the first trimester. However animal studies are insufficient with respect to effects on pregnancy/ and-or/ embryonal/foetal development/ and-or/ parturition/ and-or/ postnatal development. The potential risk for humans is unknown.

PREGABALIN

Women of child bearing potential / Contraception in males and females

As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

Pregnancy

There are no reported adequate data from the use of pregabalin in pregnant women.

Reported Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

Pregabalin is excreted into human milk. The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no reported clinical data on the effects of pregabalin on female fertility.

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

A reported fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects.

The clinical relevance of these findings is unknown.

4.7 Effects on ability to drive and use machines:

Not known

4.8 Undesirable effects:

<u>Mecobalamin</u>

Adverse reactions were reported in 13 of 2,872 patients (0.45 %). (At the end of the reexamination period)

Clinically significant adverse reactions (incidence unknown)

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.

<u>Pregabalin</u>

The pregabalin reported clinical programme involved over 8900 patients exposed to pregabalin, of whom over 5600 were in double-blind placebo-controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

Nortriptyline

Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.

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.

Class Effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose:

No reported data are available about overdosage for FDC of Pregabalin 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Film Coated Bilayered tablet in humans.

5. Pharmacological properties:

5.1 Mechanism of Action:

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

Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the

central nervous system

Mecobalamin

Mecobalamin 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.

5.2 Pharmacodynamic properties:

Mecobalamin

- Mecobalamin acts as a methyl donor for the synthesis of Lecithin, a major component of the Myelin sheath.
- Mecobalamin facilitates methylation of t-RNA which play a fundamental role in protein synthesis and stimulates methionine synthesis and helps to restore normal levels of RNA in nerve cells.
- Mecobalamin acts as a co-factor in the enzyme methionine synthase which regenerates methionine thus generating an increased supply of S-Adenosyl Methionine (SAMe) and SAMe protects from Neurotoxicity.
- Mecobalamin normalizes Nerve cell conduction by healing the damaged nerve cells and restores delayed synaptic transmission and diminished neurotransmitters to normal.
- Mecobalamin improves the excitability of the nerve fibres and thus improves the neurotransmission.

Pregabalin

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics

The active substance, pregabalin, is a gamma-aminobutyric acid analogue [(S)-3-(aminomethyl)-5-methylhexanoic acid].

Title of Study:

A reported Multicentric, Randomized, Double Blind, Parallel Group, Comparative, Phase III Clinical Study to Evaluate the Efficacy, Safety and Tolerability of FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets Versus FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets in patients with diabetic peripheral neuropathic pain with coexistent Vitamin B12 deficiency.

Study Objectives:

Primary Objective:

Evaluation of the efficacy of FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets versus FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets in patients with diabetic peripheral neuropathic pain with coexistent Vitamin B12 deficiency.

Secondary Objective:

Evaluation of the safety and tolerability of FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets versus FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets in patients with diabetic peripheral neuropathic pain with coexistent Vitamin B12 deficiency.

Methodology:

This was a multicentric, randomized, double blind, parallel group, comparative and phase III clinical study.

This study was done on male and female patients aged between 18 to 65 years (both inclusive) diagnosed with diabetic neuropathy for ≥ 6 months, total pain having intensity rating of at least 4 on a 0-10 points of numeric rating scale and decreased Vitamin B12 levels (< 200 pg/mL).

A total of 230 patients were screened out of which 210 patients were randomized by computer generated block randomization program to 84 days treatment of either of the study arm i.e., FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets (Arm A) or FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets (Arm B) in 1:1 proportion. Total patients randomized were 105 in FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets arm and 105 in FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets arm. All sites had approval from the respective Institutional Ethics Committees prior to the study initiation.

Randomized subjects were given blinded study medication i.e., either FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets or FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets and instructed to administer one tablet once a day orally every night at bedtime for 84 days. The treatment continued for the 84 days with interim follow-up on day 14±2 (V3), day 28±2 (V4) and day 56±2 (V5) from the start of treatment. The end of study visit was conducted on day 84±2 (V6). The compliance was observed through drug accountability and patient diary.

Patient's Informed consent form (ICF), demographic data and medical history were taken on screening visit/baseline visit only. Vital signs and physical examination were done at all visits.

Laboratory tests including CBC (Haemoglobin, Total RBC count, Platelet's count, Total WBC count and Differential WBC count), Total bilirubin, SGOT, SGPT, BUN, Serum creatinine, eGFR and Vitamin B12 were performed at screening visit/baseline visit (V1) and end of the study visit (V6). Also, HbA1c was performed at screening visit/baseline visit only. 12 Lead ECG was performed at all visits. Urine pregnancy test (UPT) was performed at screening/baseline visit (V1), visit 4 (V4), visit 5 (V5) and end of the study visit (V6) for all the women of child bearing potential (WOCBP). Routine urine analysis was performed at screening/baseline visit (V1) and end of the study visit (V6).

Pain intensity using numeric rating scale was performed at all visits. Neuropathic symptoms using Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale was performed at all visits. Patient global assessment and investigator global assessment were performed at end of the study visit (V6). Number of Paracetamol tablets consumed (as a rescue medication) were measured from randomization visit to all visits.

Study drug dispensing was done at visit 2 (day 1), visit 4 (day 28±2) and visit 5 (day 56±2). Patient diary was dispensed at randomization visit/visit 2 (day 1). Drug accountability was performed using patient diary and used/unused strips at visit 3 (day 14±2), visit 4 (day 28±2), visit 5 (day 56±2) and visit 6 (day 84±2)/end of the study visit. Assessment of adverse events and record of concomitant medication were done at all visits.

Independent DSMB (Data and Safety Monitoring Board) was appointed and held meetings for the review of data and patient safety on every month.

The reported data was collected on paper CRFs. The data analysis was performed for predefined parameters to correspond with the primary efficacy, secondary efficacy and safety endpoints.

Number of Patients: (Analyzed)

1. Screened: 230
2. Screen failure: 14
3. Consent withdrawn before randomization: 06
4. Randomized: 210
5. Consent withdrawn after randomization: 00
6. Lost to follow-up: 05
7. Discontinued: 00
8. Completed the study: 205

Diagnosis and main criteria for inclusion:

1. Male or female patients aged between 18 and 65 years (both inclusive).
2. Patients with diagnosis of type 2 diabetes mellitus with glycosylated hemoglobin (HbA1c) ≤11% and having pain associated with diabetic neuropathy for ≥ 6 months.
3. Patients total pain having intensity rating of at least 4 on a 0-10 points of numeric rating scale (NRS).
4. Patients with decreased Vitamin B12 levels (< 200 pg per mL).
5. Patients with ability to understand and provide written informed consent form, which must have been obtained prior to screening.
6. Patients willing to comply with the protocol requirements.

Study Assessments:

Primary Efficacy Endpoint:

Change in Numeric Rating Scale (NRS) from baseline to end of the study (12 weeks).

Secondary Efficacy Endpoints:

- Change in Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale from baseline to end of the study (12 weeks).
- Change in the Vitamin B12 levels from baseline to end of the study (12 weeks).
- Patient Global Assessment at the end of the study (12 weeks).
- Investigator Global Assessment at the end of the study (12 weeks).
- Consumption of rescue medication (number of Paracetamol Tablets consumed).

Safety End Points:

The assessment of tolerability of investigational product was based on incidence of AEs and SAEs and changes in laboratory values.

Statistical Parameters:

Statistical analysis was done using SAS 9.4. Continuous variables were statistically tested using 2-sample t-test. Categorical variables were tested using Chi-square test. Primary efficacy endpoint and secondary efficacy endpoints analysis were done using 2-sample t-test / Chi-square test. All safety parameters were analyzed using 2-sample t-test and descriptive statistics.

Efficacy Results

FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets produced statistically significant reductions in the numeric rating scale score from baseline to end of the study than FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets. No significant differences were found between two arms in vitamin B12 levels from baseline to end of the study. Number of Paracetamol Tablets consumed were significantly reduced in FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets than FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets. Patient & Investigator Global Assessment were also statistically significant in FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets than FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets.

Safety Results

For evaluation of safety, frequency of suspected, unanticipated adverse drug reactions reported possibly related to the investigational product up to end of study from start of the treatment was considered. Safety and tolerability of the test and reference products were assessed depending on the outcome from this clinical study. There were events and evidences of adverse reaction observed but were non-significant. Total 55 adverse events (AEs) were reported in 55 patients. 33 AEs were reported in FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets arm and 22 AEs were reported in FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets arm. All AEs were mild in nature. No SAE was reported during the study.

Conclusion

FDC of Pregabalin SR 75 mg + Mecobalamin 1500 mcg + Nortriptyline 10 mg Tablets produced statistically significant efficacy in mean change in numeric rating scale score from baseline to end of the study visit (week 12) when compared to FDC of Pregabalin SR 75 mg + Methylcobalamin 1500 mcg Tablets. The two treatments were safe and well tolerated. There were no deaths or hospitalizations in both the treatment groups.

5.3 Pharmacokinetic properties:

Pregabalin

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs and patients with chronic pain.

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration.

Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25-30% and a delay in t_{max} to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution

In reported preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.56 l/kg.

Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled pregabalin, approximately 98% of the radioactivity recovered in the urine was 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, there was no indication of racemisation of pregabalin Senantiomer to the R-enantiomer.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug.Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance. Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary.

Title of the Study:

In reported open label, randomized, balanced, two treatment, two sequence, two period, cross-over, single-dose oral bioequivalence study of FDC of Pregabalin SR 75mg + Nortryptyline 10mg + Mecobalamin 1500mcg Tablet (T) Manufactured by Synokem Pharmaceuticals Ltd, India with One Tablet of PREGEB M OD 75 (Pregabalin SR 75mg + Mecobalamin 1500mcg) Mfg by Torrent Pharmaceuticals Ltd and one Tablet of NORITOP 10 (Nortriptyline tablets 10 mg) (R) Manufactured by Tas Med (India) Pvt. Ltd. in normal healthy, adult male subjects under fasting condition.

Objectives:

To compare the rate and extent of absorption of Pregabalin, Nortriptyline and Mecobalamin from fixed dose combination of Pregabalin SR 75mg + Nortriptyline 10mg + Mecobalamin 1500mcg Tablet of Synokem Pharmaceuticals Ltd., India (test product) and PREGEB M OD 75 manufactured by Torrent Pharmaceuticals Ltd., and NORITOP 10 (Nortriptyline tablets 10 mg) (R) Manufactured by Tas Med (India) Pvt. Ltd. (reference product) in healthy, adult, human male subjects under fasting conditions.

To monitor the safety and tolerability of a single dose of fixed dose combination of Pregabalin SR 75mg + Nortriptyline 10mg + Mecobalamin 1500mcg Tablet in healthy, adult, human male subjects under fasting conditions.

Methodology:

Clinical personnel explained all study related procedures, duration, dates and timings, information on the study treatments and confidentiality of the subjects' data clearly to the subjects during the informed consent procedure. Subjects who signed the consent form and showed their willingness

to participate in the study were enrolled. Subjects who were eligible when assessed against the inclusion and exclusion criteria and who were found to be healthy on physical examination with laboratory investigation values within reference limits were considered for admission to the study. Subjects whose pre-study laboratory values were outside the reference range were also considered for participation provided these values were considered clinically non-significant by the investigator. The eligible subjects reported to the study site on 13Oct2020 for period 01 and on 04Nov2020 for period 02. Treatments were allocated to subjects per the randomization schedule generated using statistical techniques with SAS® (SAS Institute Inc., USA) version 9.4. Blood samples were drawn before dosing (0.00 hour) and up to 72.00 hours after dosing in each period.

Plasma concentrations of Pregabalin and Nortryptyline was analyzed using a validated LC-MS/MS method developed at Synergen Bio Pvt. Ltd., Pune, India.

Serum concentrations of Mecobalamin was analyzed using a chemiluminescent microparticle enzyme immuno-assay (MEIA) method at Synergen Diagnostics, Pune, India.

Statistical analysis was performed to assess bioequivalence between the pharmacokinetic parameters of test and reference formulations using SAS® (SAS Institute Inc., USA) version 9.4.

Diagnosis and Main Criteria for Inclusion:

Healthy, willing adult human male volunteers aged between 18 and 45 years (inclusive) were selected on the basis of laboratory evaluations during screening, demography (age, height, weight and BMI), questioning on medical history, clinical examination along with vital signs, chest X-ray (P/A view) and ECG recordings. A urine screen for drugs of abuse and an alcohol breath test were undertaken at the time of check-in of each period.

Duration of Study:

The total duration of the study was 27 days from the day of check-in of the first period till the end of the second period.

Criteria for Evaluation:

Assessment of bioequivalence was done on the basis of the 90% confidence intervals of the differences of least squares treatment means for Ln-transformed Cmax, AUC0-t and AUC0-∞ of Pregabalin and Cmax and AUC0-72h of Nortryptyline and Mecobalamin.

The acceptance criteria for bioequivalence is that the entire confidence intervals for the difference of means of Ln-transformed Cmax, AUC0-t and AUC0-∞ of Pregabalin and Cmax and AUC0-72h of Nortryptyline and Mecobalamin.should fall within 80.00 – 125.00%.

Pharmacokinetic Parameters:

Employing the estimated concentration-time profiles, the following pharmacokinetic parameters were calculated using SAS (SAS Institute Inc., U.S.A.) version 9.4.

For Pregabalin:

Primary pharmacokinetic parameters: Cmax, AUC0-t and AUC0-∞

Secondary pharmacokinetic parameters: Tmax, AUC_%, Extrap_obs, T½ and Kel.

Nortriptyline and Mecobalamin:

Primary parameters: C_{max} and AUC0-72h

Secondary parameters: T_{max}

Statistical Analysis:

Statistical analysis of the pharmacokinetic parameters were performed using SAS (SAS Institute

Inc., U.S.A.) version 9.4.

Descriptive statistics were computed and reported for the pharmacokinetic parameters. The Log-transformed pharmacokinetic parameters Cmax, AUC0-t AUC0-∞ for Pregabalin and Cmax and AUC0-72h for Nortriptyline and Mecobalamin were subjected to Analysis of Variance (ANOVA) for bioequivalence assessment. The model included sequence, subject (sequence), period and formulations effects as fixed effects factors.

For Mecobalamin, the mean of the pre-dose levels were used for the baseline adjustment of the post-dose levels. Baseline concentrations were determined for each dosing period, and baseline corrections were period specific. Wherever a negative concentration value resulted after baseline correction, this were set to 0.

Safety Assessment:

All subjects who had received at least one dose of investigational product were included in the safety evaluation. Safety assessment was based on clinical laboratory evaluation, chest X-ray (P/A view), ECG recordings, clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) measurement and post-study clinical laboratory safety evaluation. Laboratory assessments (hematology, biochemistry, serology and urine analysis), chest X-ray (P/A view) and ECG recordings were done at the time of screening. Clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure, respiratory rate) were undertaken at the time of screening, during check-in and before check-out of each period. Vital signs (axillary temperature, radial pulse rate and sitting blood pressure) were recorded within 2.50 hours prior to dosing in each period. Vital signs (sitting blood pressure and radial pulse rate) were measured and recorded at 1.00, 3.00, 5.00 and 8.00 hours after dosing (within ± 40 minutes of the scheduled time). A urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, marijuana, cocaine and morphine) and a breath test for alcohol consumption were done during check-in of each period. Subjects were questioned for well-being at the time of clinical examination and recording of vital signs.

Clinical examination, measurement of vital signs and questioning for well-being was performed prior to check-out only for the subjects who were dosed.

A safety sample was collected for post-study safety assessment (hematology and biochemistry) from all dosed subjects at the end of the study except subject no. 15. Subject no. 15 did not report to the clinical facility for post study safety sample even after repeated attempts of contact and hence was considered as lost to follow up.

A) Pharmacokinetic and Statistical Evaluation:

PREGABALIN

Table A: Descriptive Statistics of Formulation Means for Pregabalin obtained by a Non-Compartmental Model (N = 23)

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
C_{max} (ng/mL)	1424.0488 ± 492.86971	1398.3206 ± 474.48482
AUC_{0-t} (ng.hr/mL)	15092.6682 ± 5313.70872	15358.5834 ± 5672.07608
$AUC_{0-\infty}$ (ng.hr/mL)	16293.8619 ± 5604.93673	16194.9481 ± 5813.54343
K_{el} (hr^{-1})	0.1142 ± 0.02870	0.1195 ± 0.03496
$t_{1/2}$ (hr)	6.4523 ± 1.62774	6.2947 ± 1.85936

T_{max} (hr)	3.848 ± 0.7141	3.287 ± 0.7991
Extrapolated AUC (%)	7.387 ± 5.3336	5.548 ± 2.7680
	Median	
T_{max} (hr)	4.00 (3.00 - 5.00)	3.00 (1.00 - 4.53)

Table B: Geometric Least Squares Means, Ratios, 90% Confidence Intervals and ISCV for Pharmacokinetic Parameters (Cmax, AUC0-t and AUC0-□) of Pregabalin (N = 23)

Parameters (Units)	Ln- transformed			90% Confidence Interval (Parametric)		ISCV (%)
	Geometric Least Squares Mean					
	Test Product	Reference Product	T/R (%)	Lower	Upper	
Cmax (ng/mL)	1343.076	1316.919	101.99	97.62	106.54	8.62
AUC0-t (ng.hr/mL)	14220.952	14331.718	99.23	95.25	103.37	8.07
AUC0-	15377.757	15179.526	101.31	97.82	104.92	6.91

NORTRYPTYLINE

Table C: Descriptive Statistics of Formulation Means for Nortriptyline obtained by a Non-Compartmental Model (N = 23)

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
C_{max} (ng/mL)	13.8406 ± 2.35618	13.7420 ± 3.73915
AUC_{0-72h} (ng.hr/mL)	586.9387 ± 138.46216	547.6230 ± 188.72635
T_{max} (hr)	6.913 ± 2.7947	8.109 ± 3.2472
	Median	
T_{max} (hr)	5.50 (4.50 - 12.00)	6.00 (4.50 - 12.00)

Table D 90% Confidence Intervals and ISCV for Pharmacokinetic Parameters (C_{max} and AUC_{0-72h}) of Nortriptyline (N = 23)

Parameters (Units)	Ln- transformed			90% Confidence Interval		ISCV (%)
	Geometric Least Squares Mean					
	Test Product	Reference Product	T/R (%)	Lower	Upper	
Cmax (ng/mL)	13.625	13.303	102.42	95.53	109.80	13.77
AUC0-72h	560.239	527.232	94.11	82.71	107.08	25.83

MECOBALAMIN

Table E: Descriptive Statistic eans for Mecobalamin obtained by a Non- Compartmental Model (N = 23)

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
C_{max} (pg/mL)	851.3246 ± 339.49377	850.1747 ± 319.30612
AUC_{0-72h} (pg.hr/mL)	22879.7339 ± 10206.72904	22615.6861 ± 12586.57008
T_{max} (hr)	4.217± 3.0145	5.383± 9.6813
	Median	
T_{max} (hr)	4.000 (1.000 - 12.000)	3.000 (1.000 - 48.280)

Table F 90% Confidence Intervals and ISCV for Pharmacokinetic Parameters (C_{max} and AUC_{0-72h}) of Mecobalamin (N = 23)

Parameters (Units)	Ln- transformed Geometric Least Squares Mean			90% Confidence Interval		ISCV (%)
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper	
C_{max} (pg/mL)	782.279	787.145	99.38	90.47	109.17	18.66
AUC_{0-72h} (pg.hr/mL)	20620.726	20106.140	102.56	84.85	123.96	38.65

B) Safety Evaluation:

No reported serious or life-threatening adverse events were reported during the course of the study.

The incidence of adverse events (AEs), both overall and IMP-related, was low for both parts of the study.

Five (05) adverse events were observed in the study in subject nos. 02, 11, 20, 21 and 24 during post-study clinical laboratory safety evaluation (clinically significant changes in laboratory parameters).

Clinically significant laboratory abnormalities (documented as adverse events) detected during the post-study clinical laboratory safety evaluation were increased SGOT and SGPT (03 subjects, 6.38%), increased SGPT (01 subject, 2.12%) and increased total bilirubin (01 subject, 2.12%). These adverse event was detected during the end of study safety analysis and could not be attributed to either the test (T) or the reference (R) product. Hence, adverse event associated with post-study laboratory result was imputed to both formulations.

All adverse events were mild in intensity and 'unlikely' related to investigational products.

Subject nos. 02, 11, 20, 21 and 24 did not report to the clinical facility even after repeated attempts of contact and hence were classified as lost to follow up.

The test product (T) was found to be safe and well tolerated upon administration of single dose of FDC of Pregabalin SR 75mg + Nortriptyline 10mg + Mecobalamin 1500mcg Tablet in healthy adult human male subjects under fasting conditions.

Conclusion:

The 90% confidence intervals of the differences of least squares means for the Ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Pregabalin and Cmax and AUC0-

72h of Nortriptyline and Mecobalamin is within the bioequivalence acceptance limits of 80.00 - 125.00%.

Hence, it is concluded that the test product (T) FDC of Pregabalin SR 75mg + Nortryptyline 10mg + Mecobalamin 1500mcg Tablet of Synokem Pharmaceuticals Ltd., India and reference product (R) PREGEB M OD 75 (Pregabalin Sustained Release 75mg And Methylcobalamin Tablets 1500mcg) Manufactured by: TORRENT PHARMACEUTICALS LTD. 32 No. Middle Camp, NH-10, East District, Gangtok, Sikkim-737135 and NORITOP 10 (Nortriptyline Tablets I.P. 10 mg) Manufactured by: Tas Med (India) Pvt. Ltd., Plot No-8 Phase IV. Industrial Area HIMUDA, Bhatoli Kalan, Baddi, Distt. Solan (H.P.)-173205 are bioequivalent with respect to rate and extent of absorption.

6. Nonclinical properties:

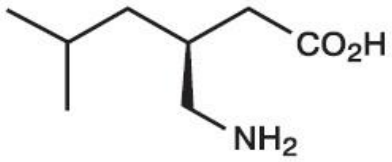
6.1 Animal Toxicology or Pharmacology

Not available

7. Description:

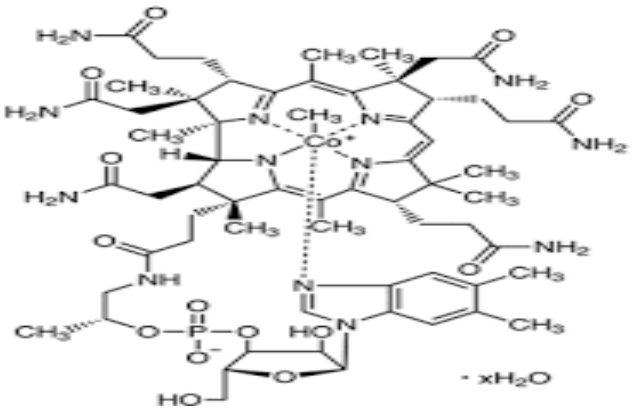
Pregabalin

Pregabalin is described chemically as (S)-4-amino-3-(2-methylpropyl) butyric acid. Pregabalin is a white to off-white powder. The molecular formula is $C_8H_{17}NO_2$ and the molecular weight is 159.23. The chemical structure of pregabalin is:



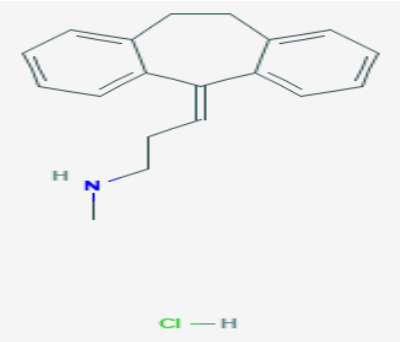
Methylcobalamin.

Methylcobalamin is coα-[α-(5,6-dimethyl-1H-benzoimidazole-1-yl-]-coβ-methylcobalamide. Methylcobalamin is a dark red crystalline powder. The molecular formula is $C_{63}H_{91}CoN_{13}O_{14}P$ and the molecular weight is 1344.4. the structural formual is:



Nortriptyline

Nortriptyline Hydrochloride is 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohept-5-ylidene)-propyl(methyl)amine hydrochloride. Nortriptyline Hydrochloride is white to off-white powder; odour slight and characteristic The molecular formula is $C_{19}H_{21}N.HCl$ and the molecular weight is 299.8. The structural formula is:



PREGABA-MNT Tablets are one side white and other side orange to light orange coloured, round, biconvex, bi-layered, film coated tablets, plain on both side. The excipients used are Crospovidone, Colloidal Silicon Dioxide, Hydroxy Propyl Cellulose, Starch 1500, Microcrystalline Cellulose, Sodium Stearyl Fumarate, Hydroxy Propyl Methyl Cellulose, Lactose, Isopropyl Alcohol, Colloidal Silicone Dioxide, Methylene Dichloride, Sunset Yellow Lake.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

None stated.

8.2 Shelf life:

Do not use later than date of expiry.

8.3 Packaging information:

PREGABA-MNT is available in 10 tablets

8.4 Storage and handing instructions:

Store at a temperature not exceeding 30°C, protected from light & moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

PREGABA-MNT

Pregabalin (Prolonged Release), Methylcobalamin and Nortriptyline Hydrochloride Tablets

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

9.1. What PREGABA-MNT Tablets is and what it is used for

PREGABA-MNT is combination of three active substances: Pregabalin (Prolonged Release), Methylcobalamin and Nortriptyline Hydrochloride Tablets and is used for the treatment of patients with diabetic peripheral neuropathic pain with coexistent vitamin B12 deficiency.

9.2. What you need to know before you take PREGABA-MNT

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking PREGABA-MNT.

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 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.

Other medicines and PREGABA-MNT Tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Your doctor may wish to alter your dose of PREGABA-MNT.

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 reported in vivo 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 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 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).

Pregnancy, breast feeding and fertility

MECOBALAMIN

The usual precautions should be observed when administering drugs during pregnancy, especially in the first trimester. However animal studies are insufficient with respect to effects on pregnancy/ and-or/ embryonal/foetal development/ and-or/ parturition/ and-or/ postnatal development. The potential risk for humans is unknown.

PREGABALIN

Women of child bearing potential / Contraception in males and females

As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

Pregnancy

There are no adequate data from the use of pregabalin in pregnant women.

Studies in reported animals have shown reproductive toxicity. The potential risk for humans is unknown.

Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

Breast-feeding

Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on newborns/infants is unknown.A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no reported clinical data on the effects of pregabalin on female fertility.

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

A reported fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects.

The clinical relevance of these findings is unknown.

9.3. How to take PREGABA-MNT Tablets

Once a daily Pregabalin (PR) 75 mg + Nortriptyline Hydrochloride 10 mg + Mecobalamin 1500 mcg film coated bilayered tablet or as directed by the Physician

It must be taken orally.

9.4. Possible side effects.

Mecobalamin

Adverse reactions were reported in 13 of 2,872 patients (0.45 %). (At the end of the reexamination period)

Clinically significant adverse reactions (incidence unknown)

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 pregabalin clinical programme involved over 8900 patients exposed to pregabalin, of whom over 5600 were in double-blind placebo-controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

Nortriptyline

Included in the following list are a few adverse reactions that have not been reported with this specific drug. However, the pharmacological similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when nortriptyline is administered.

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.

Class Effects: Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRs and TCAs. The mechanism leading to this risk is unknown

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5. How to store PREGABA-MNT TABLETS

Store at a temperature not exceeding 30°C, protected from light & moisture.

9.6. Contents of the pack and other information.

What PREGABA-MNT Tablets contains

The active substances in PREGABA-MNT tablets is Pregabalin (Prolonged Release), Methylcobalamin and Nortriptyline Hydrochloride Tablets.

The excipients used are Crospovidone, Colloidal Silicon Dioxide, Hydroxy Propyl Cellulose, Starch 1500, Microcrystalline Cellulose, Sodium Stearyl Fumarate, Hydroxy Propyl Methyl Cellulose, Lactose, Isopropyl Alcohol, Colloidal Silicone Dioxide, Methylene Dichloride, Sunset Yellow Lake.

Contents of the pack: PREGABA-MNT is available in 10 tablets

10. Details of manufacturer

Synokem Pharmaceutical Ltd

Plot No. 56-57, Sector-6A,

I.I.E. (SIDCUL), Ranipur (Bhel),

Haridwar – 249403 (Uttarakhand)

11. Details of permission or licence number with date

27/UA/SC/P-2018 issued on 30.03.2022

12. Date of revision

Not applicable

MARKETED BY

torrent PHARMA