SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pregabalin 75mg/150 mg and Methylcobalamin 750 mcg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains
Pregabalin USP 75mg/150 mg
Methylcobalamin JP 750 mcg

3. PHARMACEUTICAL FORM

Hard gelatin capsule

Appearance:

For 75/750:

Off white to pink colored Granular powder filled in Size " 2" Hard gelatin capsules having Grey Opaque body and Grey opaque cap imprinted" MP3" with black ink. The body is also marked with black band.

For 150/750:

Off white to pink colored Granular powder filled in Size " 1" Hard gelatin capsules having Brown Opaque body and Brown opaque cap imprinted " MP2" with black ink. The body is also marked with black band.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pregabalin and Methylcobalamin Capsules is a fixed-dose combination product of pregabalin and Methylcobalamin. It is intended for the treatment of painful peripheral neuropathic conditions. Painful neuropathy is characterised by chronic severe pain due to sustained nerve damage. Pregabalin has been shown to alleviate neuropathic pain and Methylcobalamin is beneficial for peripheral nerve damage. which Is a pathological hallmark of neuropathy.

Pregabalin is the S enantiomer of 3-(aminomethyl)-5-methylhexanoic acid, an analogue of gamma-aminobutyric acid (GABA), the primary inhibitory neurotransmitter in the central nervous system. The molecular formula is $C_8H_{12}NO_2$ and the molecular weight is 159.23.

Methylcobalamin is the active coenzyme form of vitamin B12 essential for the synthesis of methionine and S-adenosylmethionine that are needed for the integrity of myelin sheath of the nerves.

Experimental evidence indicates that **Methylcobalamin** may be effective in correcting the neurological defects in diabetic, alcoholic, and other forms of peripheral neuropathy.

Pregabalin and Methylcobalamin Capsules is indicated for the management of painful neuropathic conditions, Viz diabetic peripheral neuropathy and postherpetic neuralgia in adults. It is also indicated for the treatment of alcoholic neuropathy, neuropathy associated with nutritional deficiency and drug induced neuropathy in adults.

4.2 Posology and method of administration Posology

Pregabalin and Methylcobalamin Capsules is given orally without food. If Pregabalin and Methylcobalamin Capsules is reduce, discontinued or substituted with an alternative medication this should be done gradually over a minimum of 1 week.

In adult patients with a creatinine clearance rate (CL_{CR}) of at least 60 mL/min treatment for neuropathic pain is initiated with one capsule of Pregabalin and Methylcobalamin Capsules given orally twice daily for the first 3-7 days (total pregabalin dose 150 mg/day). After this period dose may be increased to one capsule of Methylcobalamin Capsules given orally twice daily (total Pregabalin dose 300 mg/day), based on individual patient response and tolerability. Patients who do not experience sufficient pain relief following 2 to 4 weeks of treatment with one capsule of Pregabalin and Methylcobalamin 150 mg given orally twice daily, and who have tolerated the dose well may be treated with up to two Pregabalin and Methylcobalamin 150 mg capsules (or one Pregabalin and Methylcobalamin 300 mg capsule) twice daily (total pregabalin dose 600 mg/day). Dosing at this level should be reserved only for those patients who have ongoing pain and are tolerating well one Pregabalin and Methylcobalamin 150 mg capsule daily.

In renally impaired adults, pregabalin and Methylcobalamin Capsules mg should be administered in reduced dosage as mentioned below.

In adults with a CL_{CR} of 30-60 mL/min the initial dose is one capsule of Pregabalin and Methylcobalamin 75 mg once daily that if required, may be increased at appropriate intervals as described above to one capsule of Pregabalin and Methylcobalamin 75 mg twice daily and finally to a maximum of one capsule of Pregabalin and Methylcobalamin 150 mg twice daily. Pregabalin and Methylcobalamin capsules are not suitable for administration if CL_{CR} is less than 30 mL/min.

4.3 Contraindications

Pregabalin and Methylcobalamin Capsules should not be given to anyone with known hypersensitivity to pregabalin, Methylcobalamin or to any other ingredients present in the formulation.

4.4 Special warnings and precautions for use

withdrawal: Discontinuation of Pregabalin and Methylcobalamin should be done over a minimum of 1 week

Tumorgenic potential: In life time carcinogenicity study in mice pregabalin was associated with a high incidence of hemangiosarcoma.

The clinical significance of this is unknown

Pregabalin present in pregabalin and Methylcobalamin Capsules mg may cause dizziness somnolence, blurred vision and other central nervous system (CNS) signs and symptoms patient should be advised not to drive vehicle, operate machinery, or engage in other hazardous activities until they have gained sufficient experience on pregabalin and Methylcobalamin Capsules mg whether or not it affects their mental, visual or motor performance adversely.

Pregabalin may cause visual disturbances patients should be informed that if changes in vision occur, they should notify their physician.

pregabalin and Methylcobalamin Capsules mg should be taken as prescribed abrupt or rapid discontinuation may result in insomnia, nausea, headache, or diarrhea.

Pregabalin may cause edema and weight gain. patients should be advised that concomitant treatment with pregabalin and Methylcobalamin Capsules mg 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.

Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. patients who require concomitant treatment with CNS depressants such as opioids or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

consuming alcohol while taking pregabalin and Methylcobalamin Capsules mg should be avoided as pregabalin may potentiate the impairment of motor skills and sedation of alcohol.

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast feeding or intend to breast feed during therapy. men being treated with pregabalin and

Methylcobalamin Capsules mg who plan to father a child should be informed of the potential risk of male-mediated teratogenicity. In preclinical studies in rats, pregabalin was associate with an increased risk of male -mediated teratogenicity.

The clinical significance of this finding is uncertain Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with pregabalin and Methylcobalamin Capsules mg. some animal treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with pregabalin was observed in clinical trials.

The use of Methylcobalamin in deficiency states or to treat any medical condition requires medical supervision. A typical dose as nutritional supplements used by pregnant women and nursing mothers is 12 mcg daily. Pregnant women and nursing mothers should only use doses higher than this if recommended by their physicians. Administration of doses greater than 10mcg daily may produce a hematological response in those with anemia secondary to folate deficiency.

Pregabalin: carcinogenesis, mutagenesis, impairment of fertlility

Carcinogenesis: 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 450 mg/kg in males and 100, 300, or 900 mg/kg in females)

Mutagenesis: Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro, was* not lactogenic in mammalian systems in vitro an ***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 (50to 2500 mg/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 fetal body weights, and an increased incidence of fetal 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 600 mg/day in addition ,adverse effects on reproductive organ (testes,epididymides) histopathology were observed in male rats exposed to pregabalin (500 to1200 mg/kg) in general toxicology studies of four weeks or greater duration .The no effect dose for male reproductive organ histopathology in rats [250 mg/kg] was associated with a plasma exposure

approximately 5 times human exposure at the MRD

In a fertlility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg orally prior to and during mating and gestation disrupted estrous cyclicity and increased number of days to mating were seen at all doses, embrolethality 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.

Human Data: In a double blind, placebo controlled clinical trials to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo and pregabalin treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Paediatric Use: Not recommended.

Generic Use: Because Pregabalin is eliminated primarily by renal excretion, the dose of pregabalin and Methylcobalamin Capsules mg should be adjusted for elderly patients with renal impairment.

4.5 Interaction with other medicinal products and other forms of interaction

DRUG INTERACTIONS

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.

Accordingly, in *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 lopiramate had no clinically significant effect on pregabalin clearance.

Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either substance.

Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration, Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may

potentiate the effects of ethanol and lorazepam.

No clinically relevant drug interactions have been described for **Methylcobalamin.**

4.6 Fertility, pregnancy and lactation

Pregnancy: There are no adequate and well-controlled studies in pregnant women, pregabalin and Methylcobalamin Capsules mg should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Breast-feeding is avoidable if taking pregabalin and Methylcobalamin Capsules mg.

4.7 Effects on ability to drive and use machines

Not applicable

4.8 Undesirable effects

Pregabalin is usually well tolerated. Adverse effects are nonserious in nature and generally mild to moderate in intensity. The common adverse reactions are: dizziness, somnolence, dry mouth, asthenia, amblyopia, peripheral adema, abnormal thoughts, weight-gain, difficulty with concentration or attention, blurred vision, and constipation.

Reporting of suspected adverse reactions

'Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions to the National Regulatory Agents.

4.9 Overdose

There is limited experience with 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. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (≥900 mg) were not clinically different from those of patients administered recommended doses of pregabalin.

There is no specific antidote for overdose with pregabalin, if indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed 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. Hemodialysis

results in significant clearance of pregabalin (approximately 50 % in 4 hours) and may be required in some cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pregabalin has a similar pharmacological profile to that of gabapentin. It demonstrated antiallodynic and antihyperalgesic activities in various rodent models of neuropathic pain, including vincristine, streptozocin and nerve injury-induced mechanical allodynia: formalin, carrageenan substance P, NMDA- and thermal injury induced hyperalgesia and surgically induced mechanical allodynia.

The exact mechanism of action of Pregabalin is unclear, it is a structural analogue of GABA, like gabapentin, although neither compound interacts with GABA -A or B-receptors, or influences GABA uptake.

Pregabalin (and gabapentin) may, however, modulate the presynaptic release of excitatory neurotransmitters, such as glutamate and noradrenaline (norepinephrine) by selectively binding with high affinity to a2-d protein, an auxillary subunit of voltage-gated calcium channels. Both Pregabalin and gabapentin modulated the release of the sensory neuropeptides substance P and calcitonin gene related peptide from rat spinal tissues, but only under conditions that correspond to significant inflammation-induced sensitization of the spinal cord. **Methylcobalamin** acts as a methyl donor for the synthesis of lecithin, a major phospholipid component of myelin sheath. Thus it promotes myelination of the nerves. It increases myelination of neurons in animal tissue culture more than cobalamide does.

Methylcobalamin promotes regeneration of the axons. It normalizes axonal skeletal protein transport in sciatic nerve cells from animal models with streptozotocin-induced diabetes mellitus. It inhibits nerve degeneration in neuropathies induced by drugs. Such as adriamycin, acrylamide, and vincristine models of axonal degeneration in mice and neuropathies in animals with spontaneous diabetes mellitus.

It restores delayed synaptic transmission and diminished neurotransmitters to normal. It restores end plate potential induction early by increasing nerve fiber excitability in crushed sciatic nerve. In addition it also normalizes diminished brain tissue levels of acetylcholine in animals fed a choline-deficient diet.

Methylcobalamin is also a co-factor in the enzyme methionine synthase, which functions to transfer methyl groups for the regeneration of methionine from homocrysteine. This helps

reverse hyperhomocystinemia that is an important risk factor for vascular disease including stroke and myocardial infraction.

Methylcobalamin is closely involved in folate metabolism that is pivotal for the synthesis of purines and pyrimidines. It promotes nucleic acid synthesis in bone marrow and promotes the maturation and division of erythroblasts there by increasing erythrocyte production and alleviating anemia.

Methylcobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis. It is better transported to nerve cell organelles than cyanocobalamin in animals. The usual adult dose is 1500 mcg daily.

5.2 Pharmacokinetic properties

Pregabalin Steady-state pharmacokinetics is 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 tested 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 admistration, 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 Cmax by approximately 25-30% and a delay in Tmax to approximately 2.5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution: In 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 id approximately 0.561/kg. Pregabalin is not bound to plasma proteins.

Metabolism: Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled 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 racemization of pregabalin S-enantiomer 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 Dosage adjustment in patients with reduced renal function or undergoing hemodialysis is necessary.

Pharmacokinetics in special patient groups

Gender : Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentration of pregabalin.

Renal impairment: Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by hemodialysis (following a 4 hour hemodialysis treatment plasma pregabalin concentrations are reduced by approximately 50

%). Because renal elimination is the major elimination pathway., dosage reduction in patient with renal impairment and dosage supplementation following hemodialysis is necessary.

Hepatic impairment: No specific pharmacokinetic studies were carried out in patients with impaired liver function, Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged drug in the urine, impaired liver function would not be expected to significantly after pregabalin plasma concentrations.

Elderly (Over 65 years of age): Pregabalin clearance tends to decrease, with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function.

Methylcobalamin absorption involves contact with 2 proteins, intrinsic factor (IF) and R proteins. In addition to absorption in the human intestine by active transport with intrinsic factor, Methylcobalamin absorption occurs by the process of passive diffusion at the rate of 1-2% of the ingested amount. Peak levels of the vitamin in the blood may not be reached for 8 to 10 hours after ingestion. Sixty to 80% of Methylcobalamin is found in the blood while small amounts are found in liver, muscle, bone, kidneys, heart, brain and spleen. It is excreted in the feces, bile and in small amounts in the urine. Human urinary excretion of Methylcobalamin is about one-third that of similar dose of cyanocobalamin, indicating substantially greater tissue retention.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol, Microcrystalline cellulose, Isopropyl alcohol, Talc, Empty hard gelatin capsule

6.2 INCOMPATIBILITIES

Not Applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30^0C. Keep out of reach of children

6.5 NATURE AND CONTENTS OF CONTAINER
Alu- Alu blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Not applicable

7.MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE

MSN LABORATORIES PRIVATE LIMITED

(Formulations Division), Plot No.

42, Anrich Industrial Estate,

Bollaram, Sangareddy District -

502 325, Telangana, INDIA

Marketing Authorization Holder "MSN Laboratories Private Limited" MSN House, Plot No.: C-24, Sanath Nagar Industrial Estate, Sanath Nagar, Hyderabad - 500 018, Telangana, India.

8.MARKETING AUTHORIZATION NUMBER
CTD13160

9.DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 April 2026

10. DATE OF REVISION OF THE TEXT

12 April 2026