

PRODUCT MONOGRAPH

MYELOGEN PG 75

(Methylcobalamin 1500mcg + Folic acid 5mg + Pyridoxine Hydrochloride 20mg +
Pregabalin 75mg SR)

For Painful Diabetic Neuropathy

Manufactured By:

Panacea Biotec Limited.

(Address as on Package)

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+ Pregabalin 75mg SR)

Tablets

For Painful Diabetic Neuropathy

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Approved Indications
Oral	One tablet of MYELOGEN PG 75 contains Methylcobalamin 1500mcg + Folic acid 5mg + Pyridoxine Hydrochloride 20mg + Pregabalin 75mg SR	Painful Diabetic Neuropathy in Adults.

INDICATIONS AND CLINICAL USE

Painful Diabetic Neuropathy in adults developed as a late manifestation of uncontrolled or long-standing diabetes that are treated with more than one antidiabetic drugs and significantly affects quality of life.

CONTRAINDICATIONS

Patients who are hypersensitive to pregabalin or any of the components of this product. Angio-oedema and hypersensitivity reactions have occurred in patients receiving pregabalin therapy.

WARNINGS AND PRECAUTIONS

Angio-oedema

There have been post-marketing reports of angioedema in patients during initial and chronic treatment with pregabalin. Specific symptoms included swelling of the face, mouth (tongue, lips, and gums), and neck (throat and larynx). There were reports of life-threatening angioedema with respiratory compromise requiring emergency treatment. Myelogen PG should be discontinued immediately in patients with these symptoms. Caution should be exercised when prescribing Myelogen PG to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angio-oedema (e.g. angiotensin-converting enzyme inhibitors) may be at increased risk of developing angio-oedema.

Hypersensitivity

There have been post marketing reports of hypersensitivity in patients shortly after initiation of treatment with pregabalin. Adverse reactions included skin redness, blisters, hives, rash, dyspnoea, and wheezing. Myelogen PG should be discontinued immediately in patients with these symptoms.

Withdrawal of Anti-Epileptic Drugs

As with all anti-epileptic drugs (AEDs), pregabalin should be withdrawn gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If Myelogen PG is discontinued, it should be tapered gradually over a minimum of 1 week.

Suicidal Behavior and Ideation

AEDs, including pregabalin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Anyone considering prescribing pregabalin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

Peripheral Oedema

Pregabalin treatment may cause peripheral oedema. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral oedema and cardiovascular complications such as hypertension or congestive heart failure. Peripheral oedema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function. Higher frequencies of weight gain and peripheral oedema were observed in patients taking both pregabalin and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering pregabalin and these agents. Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, Myelogen PG should be used with caution in these patients.

Dizziness and Somnolence

Pregabalin may cause dizziness and somnolence. Patients should be informed that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery. In the pregabalin controlled trials, both dizziness and somnolence was experienced more in the pregabalin group compared to placebo. Dizziness and somnolence generally began shortly after the initiation of pregabalin therapy and occurred more frequently at higher doses. Dizziness and somnolence were the adverse reactions most frequently leading to withdrawal.

Weight Gain

Pregabalin treatment may cause weight gain. In pregabalin controlled clinical trials, pregabalin-associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline body mass index, gender, or age. Weight gain was not limited to patients with oedema. Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown. Among diabetes patients, pregabalin was associated with higher weight gain as compared to placebo treated patients. However, the effects of this pregabalin-associated weight gain on glycaemic control have not been systematically assessed. In controlled and longer-term open label clinical trials with diabetes patients, pregabalin treatment did not appear to be associated with loss of glycaemic control (as measured by HbA1c).

Tumorigenic Potential

In clinical studies across various patient populations, comprising 6,396 patient-years of exposure in patients >12 years of age, new or worsening pre-existing tumours were reported in 57 patients. Without knowledge of the background incidence and recurrence in similar populations not treated with pregabalin, it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

Ophthalmological Effects

In controlled studies, 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. Few patients experienced reduction in visual acuity and changes in visual field and funduscopy. Less than 1% of patients discontinued pregabalin treatment due to vision-related events (primarily, blurred vision). Although the clinical significance of the ophthalmologic findings is unknown, patients should be informed that if changes in vision

occur, they should notify their physician. If visual disturbance persists, further assessment should be considered. More frequent assessment should be considered for patients who are already routinely monitored for ocular conditions.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. The relationship between the myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Patients should be instructed to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Myelogen PG treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of $20 \times 103/\mu\text{L}$, compared to $11 \times 103/\mu\text{L}$ in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and $<150 \times 103/\mu\text{L}$. A single pregabalin treated subject

developed severe thrombocytopenia with a platelet count less than $20 \times 103/\mu\text{L}$. In randomized controlled trials, pregabalin was not associated with an increase in bleeding-related adverse reactions.

PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation. In analyses of clinical trial electrocardiogram (ECG) data, the mean PR interval increase was 3–6 msec at pregabalin doses ≥ 300 mg/day. This mean change difference was not associated with an increased risk of PR increase $\geq 25\%$ from baseline, an increased percentage of subjects with on treatment PR >200 msec, or an increased risk of adverse reactions of second or third-degree atrioventricular (AV) block. Subgroup analyses did not identify an increased risk of PR prolongation in patients with baseline PR prolongation or in patients taking other PR prolonging medications. However, these analyses cannot be considered definitive because of the limited number of patients in these categories.

Effects on Ability to Drive and Use Machines

Pregabalin may have minor or moderate influence on the ability to drive and use machines. Pregabalin may cause dizziness and somnolence and, therefore, may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

Usage in pregnancy

Contraindicated

Pediatric use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Side Effects:

Pregabalin

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In all controlled and uncontrolled trials across various patient populations during the premarketing development of pregabalin, more than 10,000 patients have received pregabalin. Approximately 5,000 patients were treated for 6 months or more, over 3,100 patients were treated for 1 year or longer, and over 1,400 patients were treated for at least 2 years.

Adverse Reactions Most Commonly Leading to Discontinuation in All Premarketing Controlled Clinical Studies

In premarketing controlled trials of all populations combined, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin group, the adverse reactions most frequently leading to discontinuation were dizziness (4%) and somnolence (4%). In the placebo group, 1% of patients withdrew due to dizziness and <1% withdrew due to somnolence. Other adverse reactions that led to discontinuation from controlled trials more frequently in the pregabalin group compared to the placebo group were ataxia, confusion, asthenia, thinking abnormal, blurred vision, in coordination, and peripheral oedema (1% each). Most Common Adverse Reactions in All Premarketing Controlled Clinical Studies.

In premarketing controlled trials of all patient populations combined, dizziness, somnolence, drymouth, oedema, blurred vision, weight gain, and 'thinking abnormal' (primarily difficulty with concentration / attention) were more commonly reported by subjects treated with pregabalin than by subjects treated with placebo ($\geq 5\%$ and twice the rate of that seen in placebo). Controlled Studies with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy.

Adverse Reactions Leading to Discontinuation: In clinical trials in patients with neuropathic pain associated with diabetic peripheral neuropathy, 9% of patients treated with pregabalin and 4% of patients treated with placebo discontinued prematurely due to adverse reactions. In the pregabalin group, the most common reasons for discontinuation due to adverse reactions were dizziness (3%) and somnolence (2%). In comparison, <1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring with greater frequency in the pregabalin group than in the placebo group, were asthenia, confusion, and peripheral oedema. Each of these events led to withdrawal in approximately 1% of patients.

Other Adverse Reactions Observed During the Clinical Studies of Pregabalin

Following is a list of treatment-emergent adverse reactions reported by patients treated with pregabalin during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labelling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once, which did not have a substantial probability of being acutely life-threatening.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring on one or more

occasions in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare reactions are those occurring in fewer than 1/1,000 patients.

Body as a Whole

Frequent: Abdominal pain, allergic reaction, fever, increase in weight

Infrequent: Abscess, cellulitis, chills, malaise, neck rigidity, overdose, pelvic pain, photosensitivity reaction

Rare: Anaphylactoid reaction, ascites, granuloma, hangover effect, intentional injury, retroperitoneal fibrosis, shock

Cardiovascular System

Infrequent: Deep thrombophlebitis, congestive heart failure, hypotension, postural hypotension, retinal vascular disorder, syncope, tachycardia, atrioventricular block first degree, sinus bradycardia

Rare: ST depressed, ventricular fibrillation, QT prolongation, sinus tachycardia, sinus arrhythmia

Digestive System

Frequent: Gastroenteritis, increased appetite, vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth

Infrequent: Cholecystitis, cholelithiasis, colitis, dysphagia, oesophagitis, gastritis, gastrointestinal haemorrhage, melaena, mouth ulceration, pancreatitis, rectal haemorrhage, tongue oedema, gastro-oesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral

Rare: Aphthous stomatitis, oesophageal ulcer, periodontal abscess, ascites, pancreatitis, dysphagia

Haemic and Lymphatic System

Frequent: Ecchymosis

Infrequent: Anaemia, eosinophilia, hypochromic anaemia, leucocytosis, leukopenia, lymphadenopathy, thrombocytopenia, neutropenia

Rare: Myelofibrosis, polycythaemia, prothrombin decreased, purpura, thrombocythaemia

Metabolic and Nutritional Disorders

Infrequent: Anorexia, hypoglycaemia

Rare: Glucose tolerance decreased, urate crystalluria

Musculoskeletal and Connective Tissue Disorders

Frequent: Arthralgia, leg cramps, myalgia, myasthenia, back pain, pain in limb, cervical spasm

Infrequent: Arthrosis, joint swelling, muscle twitching, neck pain, muscle stiffness

Rare: Chondrodystrophy, generalised spasm, rhabdomyolysis

Nervous System and Psychiatric Disorders

Frequent: Anxiety, depersonalisation, hypertonia, hypoaesthesia, libido decreased, nystagmus, paraesthesia, sedation, stupor, twitching, dizziness, somnolence, headache, ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, lethargy, euphoric mood, confusion, irritability, disorientation, insomnia, paraesthesia, hypoaesthesia, sedation, balance disorder

Infrequent: Abnormal dreams, agitation, apathy, aphasia, circumoral paraesthesia, dysarthria, hallucinations, hostility, hyperalgesia, hyperesthesia, hyperkinesia, hypokinesia, hypotonia, libido increased, myoclonus, neuralgia, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, syncope, dyskinesia, malaise, hallucination, libido increased

Rare: Addiction, cerebellar syndrome, cogwheel rigidity, coma, delirium, delusions, dysautonomia, dyskinesia, dystonia, encephalopathy, extrapyramidal syndrome, Guillain-Barré syndrome, hypoalgesia, intracranial hypertension, manic reaction, paranoid reaction, peripheral neuritis, personality disorder, psychotic depression, schizophrenic reaction, sleep disorder, torticollis, trismus, convulsions, parosmia, hypokinesia, dysgraphia, disinhibition

Respiratory, Thoracic and Mediastinal Disorders

Infrequent: Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness

Rare: Apnoea, atelectasis, bronchiolitis, hiccup, laryngismus, lung oedema, lung fibrosis, yawn, pulmonary oedema, throat tightness

Skin and Appendages

Frequent: Pruritus

Infrequent: Alopecia, hyperhidrosis, dry skin, eczema, hirsutism, skin ulcer, urticaria, vesiculobullous rash, pruritis

Rare: Angioedema, exfoliative dermatitis, lichenoid dermatitis, melanosis, nail disorder, petechial rash, purpuric rash, pustular rash, skin atrophy, skin necrosis, skin nodule, Stevens-Johnson syndrome, subcutaneous nodule

Special Senses

Frequent: Conjunctivitis, diplopia, otitis media, tinnitus, vision blurred

Infrequent: Abnormality of accommodation, blepharitis, peripheral vision loss, visual acuity reduced, eye pain, asthenopia, photopsia, lacrimation increased, eye irritation, dry eyes, eye haemorrhage, eye swelling, visual field defect, hyperacusis, photophobia, retinal oedema, taste loss, taste perversion

Rare: Anisocoria, blindness, corneal ulcer, exophthalmos, extraocular palsy, iritis, keratitis, oscillopsia, altered visual depth perception, strabismus, visual brightness, keratoconjunctivitis, miosis, mydriasis, night blindness, ophthalmoplegia, optic atrophy, papilloedema, parosmia, ptosis, uveitis

Urogenital System and Breast Disorders

Frequent: Anorgasmia, impotence, urinary frequency, urinary incontinence

Infrequent: Abnormal ejaculation, albuminuria, amenorrhoea, dysmenorrhoea, dysuria, haematuria, kidney calculus, leucorrhoea, menorrhagia, metrorrhagia, nephritis, oliguria, urinary retention, urine abnormality, breast pain

Rare: Acute kidney failure, balanitis, bladder neoplasm, cervicitis, dyspareunia, epididymitis, female lactation, glomerulitis, ovarian disorder, pyelonephritis, breast discharge, breast enlargement, gynaecomastia

Infections and Infestations

Frequent: Nasopharyngitis

Vascular Disorders

Infrequent: Hypotension, hypertension, hot flushes, flushing, peripheral coldness

General Disorders and Administration Site Conditions

Frequent: Oedema, peripheral oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue

Infrequent: Generalized oedema, face oedema, chest tightness, pain, pyrexia, thirst

Investigations

Infrequent: Blood creatine phosphokinase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased.

Withdrawal Symptoms

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment. Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose related.

Post marketing Experience

The following adverse reactions have been identified during post-approval use of pregabalin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous System Disorders: Headache

Gastrointestinal Disorders: Nausea, diarrhoea

Reproductive System and Breast Disorders: Gynaecomastia, breast enlargement

In addition, there are post marketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. There are also post marketing reports of respiratory failure and coma in patients taking pregabalin and other central nervous system depressant medications.

Mecobalamin (Methylcobalamin)

Gastrointestinal

Anorexia, nausea, vomiting and diarrhoea were observed with a frequency of <5%.

Anaphylactoid Reaction

Anaphylactoid reaction such as decrease in blood pressure or dyspnoea, may occur with mecobalamin. Patients should be carefully observed. In the event of such symptoms, treatment should be discontinued immediately and appropriate measures taken.

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), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. In vitro and in vivo studies showed that pregabalin is unlikely to be involved in significant pharmacokinetic drug interactions.

In vitro Studies

Pregabalin, at concentrations that were, in general, 10 times those attained in clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems. In vitro drug interaction studies demonstrate that pregabalin does not induce CYP1A2 or CYP3A4 activity. Therefore, an increase in the metabolism of co-administered CYP1A2 substrates (e.g. theophylline, caffeine) or CYP3A4 substrates (e.g. midazolam, testosterone) is not anticipated.

In vivo Studies

The drug interaction studies described in this section were conducted in healthy adults, and across various patient populations.

Gabapentin

Gabapentin pharmacokinetics following single- and multiple-dose administration was unaltered by pregabalin co-administration. The extent of pregabalin absorption was unaffected by gabapentin co-administration, although there was a small reduction in rate of absorption.

Oral Contraceptives

Pregabalin co-administration (200 mg three times a day) had no effect on the steady-state pharmacokinetics of norethindrone and ethinyl oestradiol (1 mg/35 µg, respectively) in healthy subjects.

Lorazepam

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of lorazepam single-dose pharmacokinetics and single-dose administration of lorazepam (1 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Oxycodone

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of oxycodone single-dose pharmacokinetics. Single-dose administration of oxycodone (10 mg) had no effect on the steady-state pharmacokinetics of pregabalin.

Ethanol

Multiple-dose administration of pregabalin (300 mg twice a day) in healthy subjects had no effect on the rate and extent of ethanol single-dose pharmacokinetics and single-dose administration of ethanol (0.7 g/kg) had no effect on the steady-state pharmacokinetics of pregabalin. Regular consumption of alcohol is an important risk factor for the development and the progression of neuropathic clinical pictures and may therefore also have a negative influence on the success of treatment with this combination. For this reason, it is generally

recommended for patients suffering from diabetic neuropathy to avoid the consumption of alcohol as far as possible. This shall also apply to treatment-free intervals.

AEDs

Steady-state trough plasma concentrations of phenytoin, phenobarbital, topiramate, carbamazepine and carbamazepine 10, 11 epoxide, valproic acid, and lamotrigine were not affected by concomitant pregabalin (200 mg three times a day) administration. These drugs have no effect on the pharmacokinetics of pregabalin and pregabalin has no effect on the pharmacokinetics of the mentioned drugs. Tiagabine also had no effect on the pharmacokinetics of pregabalin.

Antidiabetic Agents

Concomitant administration of glyburide, insulin or metformin with pregabalin did not affect the pharmacokinetics of pregabalin. Additive hypoglycaemic effects may occur with concomitant use of antidiabetic agents.

Furosemide

Concomitant administration of furosemide with pregabalin did not affect the pharmacokinetics of pregabalin.

Renal impairment:

Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction. Pregabalin dosage adjustment should be considered in cases of renal impairment (refer to Dosage and Administration>>Patients with Renal Impairment)

Hepatic impairment:

No dose adjustment is required for patients with hepatic impairment.

Pregnancy:

Pregnancy Category C

Increased incidences of foetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy at doses that produced plasma pregabalin exposures (AUC) ≥ 5 times human exposure at the maximum recommended dose of 600 mg/day. There are no adequate and well-controlled studies for the use of pregabalin in pregnant women. No USFDA rating is available for pregabalin. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Lactation:

It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumourigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the combination, taking into account the importance of the drug to the mother.

Pediatric use:

Safety and effectiveness of any of the components of this product in paediatric patients have not been established.

Geriatric use:

No overall differences in safety and efficacy were observed between patients ≥ 75 years of age and younger patients. Even though the incidence of adverse events did not increase with age, greater sensitivity of some older individuals cannot be ruled out. Pregabalin is known to be substantially excreted by the kidney, and the risk of toxic reactions to pregabalin may be greater in patients with impaired renal function. Because pregabalin is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

Drug Abuse and Dependence*Controlled Substance*

Pregabalin is a Schedule V controlled substance. Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g. development of tolerance, dose escalation, and drug-seeking behaviour).

Abuse

In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, pregabalin (450 mg, single dose) received subjective ratings of “good drug effect”, “high” and “liking” to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5,500 patients, 4% of pregabalin-treated patients and 1% of placebo treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged 1–12%.

Dependence

In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhoea, consistent with physical dependence. In the post marketing experience, in addition to these reported symptoms there have also been reported cases of anxiety and hyperhidrosis.

DOSAGE AND ADMINISTRATION

Myelogen PG is given as 1 tablet per day.

Method of administration

Myelogen PG taken orally may be with or without food.

Overdosage:*Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans*

There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development programme was 8,000 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; 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. Although haemodialysis 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 haemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

Mecobalamin has excellent tolerability and no known toxicity.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Pregabalin

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 is unknown, 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 anti-seizure 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 antinociceptive 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. 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.

Mecobalamin (Methylcobalamin)

Methylcobalamin is one of two active endogenous coenzymes used by B-12 dependent enzymes in the body, and is specifically the B-12 form used by 5-methyltetrahydrofolate-homocysteine methyl transferase (MTR), also known as methionine synthase. Mecobalamin plays an important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocysteine. It also enhances the formation of lecithin (another major component of the myelin sheath).

Methylcobalamin is notable for being one of the few examples in nature of a bona fide organometallic bond.

Mecobalamin is well transported to nerve cell organelles, and promotes nucleic acid and protein synthesis. Mecobalamin is better transported to nerve cell organelles than cyanocobalamin in rats. It has been shown in experiments with cells from the brain origin and spinal nerve cells in rats to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folic acid utilization and metabolism of nucleic acid. Also, Mecobalamin promotes nucleic acid and protein synthesis in rats more than cobamamide does.

Mecobalamin promotes axonal transport and axonal regeneration. Mecobalamin normalizes axonal skeletal protein transport in sciatic nerve cells from rat models with streptozotocin-induced diabetes mellitus. It exhibits neuropathologically and electrophysiologically inhibitory effects on nerve degeneration in neuropathies induced by drugs, such as Adriamycin, acrylamide, and vincristine (in rats and rabbits), models of axonal degeneration in mice and neuropathies in rats with spontaneous diabetes mellitus.

Mecobalamin promotes myelination (phospholipid synthesis). Mecobalamin promotes the synthesis of lecithin, the main constituent of medullary sheath lipid and increases myelination of neurons in rat tissue culture more than cobamamide does.

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

Folic Acid

Folic acid is a B complex vitamin containing a pteridine moiety linked by a methylene bridge to para-aminobenzoic acid, which is joined by a peptide linkage to glutamic acid. Folic acid acts as cofactor for transformylation reactions in biosynthesis of purines and thymidylates of nucleic acids. Folic acid is required for normal nerve growth. Myelin consists of lecithin and ethanolamine. S-Adenosyl Methionine provides the methyl groups for conversion of ethanolamine to lecithin. If there is Folate deficiency, there is increased ethanolamine and less amounts of lecithin which is more important for myelin regeneration. Interference with the methylation reaction may lead to neuropathy. Folic acid deficiency may also cause axonal degeneration.

Pyridoxine Hydrochloride

The chemical name of Vitamin B6 is 2-methyl-3-hydroxy-4, 5-bis (hydroxymethyl) pyridine hydrochloride. Natural substances that have vitamin B6 activity are pyridoxine in plants and pyridoxal or pyridoxamine in animals. All these forms of vitamin B6 are converted to pyridoxal phosphate by the enzyme pyridoxal kinase. The physiologically active forms of vitamin B6 are pyridoxal phosphate (codecarboxylase) and pyridoxamine phosphate. Riboflavin is required for the conversion of pyridoxine phosphate to pyridoxal phosphate.

Vitamin B6 acts as a coenzyme in the metabolism of protein, carbohydrate, and fat. In protein metabolism, it participates in the decarboxylation of amino acids, conversion of tryptophan to niacin or to serotonin (5-hydroxytryptamine), deamination, and transamination and transulfuration of amino acids. In carbohydrate metabolism, it is responsible for the breakdown of glycogen to glucose-1-phosphate.

Pharmacokinetics

Pregabalin

Absorption

Pregabalin Following oral administration of pregabalin under fasting conditions, peak plasma concentrations occur within 1.5 hours. Pregabalin oral bioavailability is $\geq 90\%$ and is

independent of dose. Following single-dose (25–300 mg) and multiple-dose (75–900 mg/day) administration, maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values increase linearly. Following repeated administration, steady state is achieved within 24–48 hours. Multiple-dose pharmacokinetics can be predicted from single-dose data. The rate of pregabalin absorption is decreased when given with food, resulting in a decrease in C_{max} of approximately 25–30% and an increase in time at peak concentrations (T_{max}) to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total absorption of pregabalin. Therefore, pregabalin can be taken with or without food.

Distribution

Pregabalin does not bind to plasma proteins. The apparent volume of distribution of pregabalin following oral administration is approximately 0.5 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 Excretion

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 (S-enantiomer) 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 (CL_{cr}).

Mecobalamin (Methylcobalamin)

Evidence indicates mecobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of vitamin B₁₂. The quantity of cobalamin detected following a small oral dose of mecobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of mecobalamin. Human urinary excretion of mecobalamin is about one-third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention. Peak plasma concentrations occur three hours after oral administration. It is mainly excreted through the kidney.

Folic Acid

Folic acid is rapidly absorbed mainly from the duodenum and jejunum. Its peak plasma concentration is achieved within 0.5 to 1 hour. It is extensively bound to plasma protein. Principal site of storage is the liver. It is also concentrated in the CSF and enters the breast milk. Folic acid undergoes conversion in the plasma and liver to the metabolically active 5-methyltetrahydrofolate. The unchanged drug and metabolites are excreted through the urine.

Pyridoxine Hydrochloride

The amount of pyridoxine in the body varies from 16 to 25 mg. Its half-life ranges from 15 to 20 days. Vitamin B6 is degraded to 4-pyridoxic acid in the liver. This metabolite is excreted mainly in the urine.

STORAGE AND STABILITY

Keep out of reach or sight of children and pets.

Myelogen PG should be stored at temperature below 30°C, protect from light and moisture.

Medicines should not be disposed of down the drain or in household garbage. Ask your pharmacist how to dispose of medicines no longer

SPECIAL HANDLING INSTRUCTIONS

No special requirements.

DOSAGE FORMS: Tablets for Oral Administration

COMPOSITION:

GLIZID-M OD:	Gliclazide IP	SR 60mg
	Metformin hydrochloride IP	SR 500mg

PACKAGING:

GLIZID-M OD : 10 tablets per strip

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

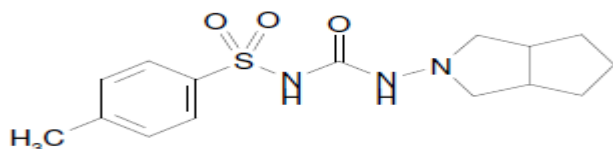
Proper name: Gliclazide

Chemical name: 1-(3-Azabicyclo [3.3.0]-oct-3-yl)-3-(p-tolylsulfonyl) urea

Molecular formula: C₁₅H₂₁N₃O₃S

Molecular mass: 323.42

Structural formula:



Physicochemical properties: Physical form: white, crystalline powder

Solubility: Practically insoluble in water; freely soluble in dichloromethane; sparingly soluble in acetone.

pKa: 5.8

Partition Coefficient:

pH %	gliclazide in organic phase(water/CHCl ₃)
0 to 7	almost 100%
8.6	80%
9.0	55%
10.0	12%

Melting Point: Approximately 168°C

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Metformin HCl

Chemical name: N, N-dimethyl biguanide hydrochloride

Molecular formula and molecular mass: 165.6

Structural formula:



Physicochemical properties:

Metformin HCl is a white crystalline powder.

Metformin HCl is soluble in water and in 95% ethyl alcohol.

It is practically insoluble in ether and in chloroform.

Melting Point: 218-220°C.

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You should know that the usual signs of low blood sugar level (hypoglycemia) are: anxious feeling, drowsiness, chills, cold sweats, confusion, cool pale skin, difficulty in concentration, excessive hunger, fast heartbeat, headache, nausea, nervousness, shakiness, unsteady walk, unusual tiredness or weakness. If you recognize by some of these signs of the drop in blood sugar, immediately eat or drink something containing sugar and notify your doctor without delay. Good sources of sugar are: orange juice, corn syrup, honey, or sugar cubes or table sugar (dissolved in water).

This product monograph, prepared for health professionals can be found at:

(Panacea Biotec Web site)

or by contacting the Panacea Biotec Limited (INDIA)

(Address for correspondence)

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