For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

GABATOR M

1. Generic Name

Gabapentin & Methylcobalamin Tablets

2. Qualitative and quantitative composition

GABATOR M 100

Each film coated tablet contains:

Gabapentin I.P. …….....100 mg

Methylcobalamin I.P. ….....500 mcg

Colour: Ferric Oxide Red USP-NF & Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose, Croscarmellose Sodium, Poloxamer 407, Pregelatinised Starch, Polyvinyl Pyrrolidone (K-30), Maize Starch, Purified water, Colloidal Silicon Dioxide, Magnesium Stearate, Isopropyl Alcohol, P.E.G.-400, H.P.M.C. (E5), Dichloromethane.

GABATOR M 300

Each film coated tablet contains:

Gabapentin I.P. …….....300 mg

Methylcobalamin I.P. ….....500 mcg

Colour: Ponceau 4R & Titanium Dioxide I.P.

The excipients used are Colloidal Silicon Dioxide, Microcrystalline Cellulose, Maize Starch, Polyvinyl Pyrrolidone (K-30), Purified water, Magnesium Stearate, Sodium Starch Glycolate, Croscarmellose Sodium, Isopropyl Alcohol, Dichloromethane, H.P.M.C. (E5), P.E.G.-400, Purified Talc.

3. Dosage form and strength

Dosage form: tablet

Strength: 100 mg +500 mcg and 300 mg+ 500 mcg

4. Clinical particulars

4.1 Therapeutic indication

GABATOR M is indicated for neuropathic pain in adults.

4.2 Posology and method of administration

Posology

Gabapentin:

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1

DOSING CHART – INITIAL TITRATION		
Day 1	Day 2	Day 3
300mg once a day	300mg two times a day	300mg three times a day

Discontinuation of gabapentin

In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

Peripheral neuropathic pain

Adults

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300mg/day increments every 2-3 days up to a maximum dose of 3600mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800mg/day is one week, to reach 2400mg/day is a total of 2 weeks, and to reach 3600mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

Instruction for all areas of indication

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

Elderly (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age. Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

Renal impairment

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin can be used to follow dosing recommendations for patients with renal insufficiency.

Table 2	
DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION	
Creatinine Clearance (ml/min)	Total Daily Dose[a] (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150[b] -600
<15[c]	150[b] -300

[a] Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79ml/min).

[b] The 150mg daily dose to be administered as 300mg every other day.

[c] For patients with creatinine clearance <15ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15ml/min receive).

Use in patients undergoing haemodialysis

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400mg, then 200 to 300mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300mg dose following each 4-hour haemodialysis treatment is recommended.

Methylcobalamin

The drug should be given as directed by the physician. The general recommended therapy is to start as one tablet, single dose, on Day 1. Two tablets (Divided b.i.d) on Day 2. And three tablets (dlvided t.i.d) on Day 3. The dose may then be uptitrated up to 2 tablets, 3 times a day. The average effective dose of methylcobalamin has been found to be 1500 mcg/day which is achieved by giving atleast 3 tablets a day.

Method of administration

For oral use.

Gabator M can be given with or without food and should be swallowed whole with sufficient fluid intake (e.g. a glass of water).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias.
- Severe liver disease.
- Mania.
- Tobacco amblyopia. Should not be used to treat megaloblastic anaemia of pregnancy. Should not be administered before perncious anaemia or folate deficiency has been ruled out.

4.4 Special warnings and precautions for use

Gabapentin

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking antiepileptic drugs including gabapentin.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Anaphylaxis

Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Cases of suicidal ideation and behaviour have been observed in patients treated with gabapentin in the post-marketing experience.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Discontinuation of gabapentin treatment should be considered in case of suicidal ideation and behaviour.

Acute pancreatitis

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered.

Seizures

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus.

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). 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.

Concomitant use with opioids and other CNS depressants

Patients who require concomitant treatment with central nervous system (CNS) depressants, including opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin or concomitant treatment with CNS depressants including opioids should be

reduced appropriately.

Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression. In a reported population-based, observational, nested case-control study of opioid users, co prescription of opioids and gabapentin was associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio [aOR], 1.49 [95% CI, 1.18 to 1.88, p<0.001]).

Respiratory depression

Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

Elderly (over 65 years of age)

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one reported double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

Paediatric population

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Abuse and Dependence

Cases of abuse and dependence have been reported in the post-marketing database. Carefully evaluate patients for a history of drug abuse and observe them for possible signs of gabapentin abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance.

Laboratory tests

False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Methylcobalamin:

The prologned use of larger doses of methylcobalamin is not recommended for patients whose occupation requires the handling of mercury or mercury compounds.

Use cautiously in patients with hypertension, cardiovascular and lung diseases. Cardiac arrhythmias secondary to hypokalaemia during initial therapy have been reported. Vitamin B12 should be given prophylactically only when there is a reasonable indication. Administration of methycobalamin doses greater than 10mcg daily, may produce a hematological response in patients with folate deficiency. It is important to monitor methylcobalamin concentrations in plasma and to obtain peripheral blood counts at intervals of 3 to 6 months to confirm that adequacy of therapy. Since refractoriness to therapy can develop at any time, evaluation must continue throughout the patient's life. Serum concentrations may be decreased by concurrent administration of oral contraceptives. Blood

concentrations of methylcobalamin may be reduced if large doses of folate are taken continuously.

4.5 Drugs interactions

Gabapentin

There are spontaneous and literature case reports of respiratory depression and/or sedation and death associated with gabapentin when co-administered with CNS depressants, including opioids. In some of these reports, the authors considered the combination of gabapentin and opioids to be a particular concern in frail patients, in the elderly, in patients with serious underlying respiratory disease, with polypharmacy, and in those with substance abuse disorders.

In a reported study involving healthy volunteers (N=12), when a 60mg controlled-release morphine capsule was administered 2 hours prior to a 600mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

Co-administration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Co-administration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is co-administered with cimetidine is not expected to be of clinical importance.

Methylcobalamin:

Tetracycline: Vitamin B12 should not be taken at the same time as the antibiotic Tetracycline because it Interferes with the absorption and effectiveness of this medication. Vitamin B12 either alone or in combinatin with other B vitamins should be taken at different times of the day from tetracycline.

Chemotherapy Medications: Blood levels of Vitamin B12 may be reduced when taking chemotherapy medications (particularly methotrexate) for cancer.

Absorption of cobalamin is impaired by alcohol, vitamin B6 (pyridoxine) deficiency, cholestyramine, para-aminosalicylic acid colchicines, neomycin, the oral bigunades, metformin, histamine H2 receptor antagonists (clmetidine, ranitidine, etc.) phenformin and possibly potassium chloride. A number of anticonvulsants phenobarbitone, primidone, phenytoin, and ethylphenacemide can alter the metabolism of cobalamin in the cerebrospinal fluid and lead to neuropsychotic disturbances. Several substituted amide, lactone and lactum analogues of cyanocobalamin compete with binding sites on intrinsic factor and lead to depressed absorption of the vitamins. Nitrous oxide also interferes with cobalamin metabolism.

4.6 Use in special populations

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely.

It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk related to gabapentin.

Gabapentin crosses the human placenta.

There are no or limited amount of data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is causally associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Breast-feeding

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

Fertility

There is no effect on fertility in animal studies.

4.7 Effects on ability to drive and use machines

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms.

Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

4.8 Undesirable effects

Gabapentin

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency (very common (> 1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10,000; <1/1,000); very rare (<1/10,000). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Additional reactions reported from the post-marketing experience are included as frequency 'Not known' (cannot be estimated from the available data) in italics in the list below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Adverse drug reactions**
Infections and infestations	
Very Common	viral infection
Common	pneumonia, respiratory infection, urinary tract infection, infection, otitis media
Blood and the lymphatic system disorders	
Common	leucopenia
Not known	*Thrombocytopenia*
Immune system disorders	
Uncommon	allergic reactions (e.g. urticaria*)*
Not known	*hypersensitivity syndrome (a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms), anaphylaxis (see section 4.4)*
Metabolism and nutrition disorders	
Common	anorexia, increased appetite
Uncommon	hyperglycaemia (most often observed in patients with diabetes)
Rare	hypoglycaemia (most often observed in patients with diabetes)
Not known	*hyponatraemia*
Psychiatric disorders	
Common	hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Uncommon	agitation
Not known	hallucinations, suicidal ideation
Nervous system disorders	
Very Common	somnolence, dizziness, ataxia
Common	convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon	hypokinesia, mental impairment
Rare	loss of consciousness
Not known	*other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)*
Eye disorders	

Common	visual disturbances such as amblyopia, diplopia
Ear and labyrinth disorders	
Common	vertigo
Not known	*tinnitus*
Cardiac disorders	
Uncommon	palpitations
Vascular disorders	
Common	hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	
Common	dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Rare	respiratory depression
Gastrointestinal disorders	
Common	vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Uncommon	dysphagia
Not known	*pancreatitis*
Hepatobiliary disorders	
Not known	*hepatitis, jaundice*
Skin and subcutaneous tissue disorders	
Common	facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Not known	*Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see section 4.4)*
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, back pain, twitching
Not known	*rhabdomyolysis, myoclonus*
Renal and urinary disorder	
Not known	*acute renal failure, incontinence*
Reproductive system and breast disorders	
Common	impotence
Not known	*breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)*
General disorders and administration site conditions	
Very Common	fatigue, fever
Common	peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon	generalized oedema
Not known	*withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not*

	been established.
Investigations	
Common	WBC (white blood cell count) decreased, weight gain
Uncommon	elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin
Not known	*blood creatine phosphokinase increased*
Injury, poisoning and procedural complications	
Common	accidental injury, fracture, abrasion
Uncommon	fall

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear.

In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children.

Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

Methylcobalamin:

Generally well tolerated.

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

Gabapentin

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy and mild diarrhoea.

All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Although gabapentin can be removed by haemodialysis, based on prior experience it is usually not required.

However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000mg/kg.

Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

Methylcobalamin:

No such case have been described in the literature and it is unlikely that any harm would result.

5. Pharmacological properties

5.1 Mechanism of action

Gabapentin

Mechanism of action

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either GABAA or GABAB receptor nor does it alter the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with high affinity to the α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than α2δ.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to α2δ through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

Gabapentin also displays efficacy in several pre-clinical animal pain models. Specific binding of gabapentin to the α2δ subunit is proposed to result in several different actions that may be responsible for analgesic activity in animal models. The analgesic activities of gabapentin may occur in the spinal cord as well as at higher brain centres through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

Methylcobalamin:

Vitamin B12 is necessary for the formation of blood corpuscles, nerve sheaths and various proteins. It is also involved in fat and carbohydrate metabolism and is essential for growth. Adenosylcobalamin is the co enzyme for isomerization of 1-Methylmalonyl Co enzyme A to Succinyl Coenzyme A (an important reaction in lipid and carbohydrate metabolism) and in Ribonucleotide reduction (which provides building blocks for DNA synthesis). Reactions involving methylcobalamin include biosynthesis of methionine, methane and acetate. There is evidence that Vitamin B12 is required the synthesis of folate polyglutamase (active coenzyme required in the formation of nerve tissue) and in the regeneration of folate during red blood cell formation. Methylcobalamin is an endogenous Coenzyme B12 Methylcobalamin plays as important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocystnine.

5.2 Pharmacodynamics properties

Gabapentin

Clinical efficacy and safety

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-

hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years). The data from this additional post-hoc analysis are summarised in the table below:

Response (≥ 50% Improved) by Treatment and Age MITT* Population			
Age Category	Placebo	Gabapentin	P-Value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

Methylcobalamin:

Methylcobalamin is well transporter to nerve cells organelles, and promotes nucleic acid and protein synthesis in animal studies: Methylcobalamin was shown to be better transporter to nerve cell organelles than cyanocobalamin.

It has also been shown in experiments with cells from the brain origin and spinal nerve calls to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folate utilization and metabolism of nucleic acid. Also, methylcobalamin plays role in nucleic acid and protein synthesis more than adenosylcobalamin does.

Methylcobalamin promotes axonal transport and axonal regeneration: Methylcobalamin 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, models of axonal degeneration in mice and neuropathies in rats with spontaneous diabetes mellitus.

Methylcobalamin promotes myelination (phospholipids synthesis): Methylcobalamin promotes the synthesis of lecithin, the main constituent of medullary sheath lipids, and increases myelination of neurons in tissue culture more than adenosylcobalsmin does. Methylcobalamin resotes delayed synaptic transmission and diminished neurotransmitters to normal in animal studies: methylcobalamin restores end-plate potential induction early by addition, methylcobalamin normalizes diminished brain tissue levels of acetyl choline in rats fed a choline dificient diet.

5.3 Pharmacokinetic properties

Gabapentin

Absorption:

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours.

Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2µg/ml and 20µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3

Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300mg (N = 7)		400mg (N = 14)		800mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
C_{max} (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
t_{max} (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T1/2 (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) µg•hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

C_{max} = Maximum steady state plasma concentration
t_{max} = Time for C_{max}
T1/2 = Elimination half-life
AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose
Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose
NA = Not available

Distribution:

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Biotransformation:

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Excretion:

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced.

Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended.

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

In a reported pharmacokinetic study in 24 healthy paediatric subjects aged between 1 month and 48 months, an approximately 30% lower exposure (AUC), lower Cmax and higher clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

Methylcobalamin

Evidence indicates methylcobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of Vitamin B12 Experiments have demonstrated similar absorption of methylcobalamin following oral administration. The quantity of cobalamin detected following a small oral dose of methylcobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of methylcobalamin. Human urinary excretion of methylcobalamin is about one third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000mg/kg/day and to rats at 250, 1000, and 2000mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumours was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000mg/kg/day are 10 times higher than plasma concentrations in humans given 3600mg/day. The pancreatic acinar cell tumours in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumours in male rats to carcinogenic risk in humans is unclear.

Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic in vitro in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells in vitro or in vivo, and did not induce micronucleus formation in the bone marrow of hamsters.

Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000mg/kg (approximately five times the maximum daily human dose on a mg/m2 of body surface area basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600mg, (four, five or eight times, respectively, the human daily dose on a mg/m2 basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hind limbs in rodents, indicative of foetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000mg/kg/day during organogenesis and in rats given 2000mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600mg on a mg/m2 basis.

No effects were observed in pregnant mice given 500mg/kg/day (approximately 1/2 of the daily human dose on a mg/m2 basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000mg/kg/day in a fertility and general reproduction study, 1500mg/kg/day in a teratology study, and 500, 1000, and 2000mg/kg/day in a perinatal and postnatal reported study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m2 basis.

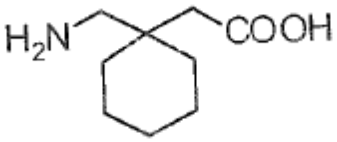
There are some reports of neurodegenerative changes in the brains of offspring exposed to gabapentin during pregnancy from rodent studies published in the open literature. However, limitations in study designs means the toxicological significance and clinical relevance of these findings are unclear. A GLP compliant perinatal and postnatal reported study in rats showed reversible behavioural changes in offspring exposed to 1000 mg/kg gabapentin (approximately 1 to 5 times the human does of 3600 mg on a mg/m2 basis) from GD15 to PND21. Overall, the available data is insufficient to determine the developmental neurotoxic potential of gabapentin.

In a reported teratology study in rabbits, an increased incidence of post-implantation foetal loss, occurred in pregnant rabbits given 60, 300, and 1500mg/kg/day during organogenesis. These doses are approximately 0.3 to 8 times the daily human dose of 3600mg on a mg/m2 basis. The margins of safety are insufficient to rule out the risk of these effects in humans.

7. Description

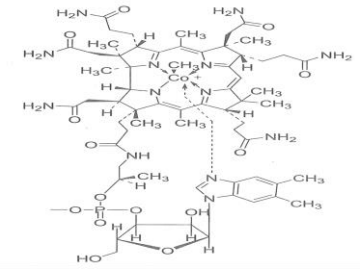
Gabapentin

Gabapentin is [1-(aminomethyl) cyclohexyl] acetic acid. The empirical formula is $C_9H_{17}NO_2$ and its molecular weight is 171.2 g/mol. The chemical structure of Gabapentin is:



Methylcobalamin

Methylcobalamin is Coα-[α-(5,6-dimethyl-1H-benzoimidazole-1-yl)-Coβ-methylcobamide. The empirical formula is $C_{63}H_{91}CoN_{13}O_{14}P$ and its molecular weight is 1344.4 g/mol. The chemical structure of Methylcobalamin is:



GABATOR M 100 is reddish brown coloured, round, biconvex, film coated tablets, plain on both side. The excipients used are Microcrystalline Cellulose, Croscarmellose Sodium, Poloxamer 407, Pregelatinised Starch, Polyvinyl Pyrrolidone (K-30), Maize Starch, Purified water, Colloidal Silicon Dioxide, Magnesium Stearate, Isopropyl Alcohol, P.E.G.-400, H.P.M.C. (E5), Dichloromethane.

GABATOR M 300 is red coloured, round, biconvex, film coated tablets, Scored on one side and plain on other side. The excipients used are Colloidal Silicon Dioxide, Microcrystalline Cellulose, Maize Starch, Polyvinyl Pyrrolidone (K-30), Purified water, Magnesium Stearate, Sodium Starch Glycolate, Croscarmellose Sodium, Isopropyl Alcohol, Dichloromethane, H.P.M.C. (E5), P.E.G.-400, Purified Talc.

8. Pharmaceutical particulars

8.1 Incompatibilities

None Stated

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

GABATOR M is packed in blister strip of 10 tablets

8.4 Storage and handing instructions

Store Protected from light & moisture, at a temperature not exceeding 25°C.

Keep out of reach of children.

9. Patient Counselling Information

Package leaflet: Information for the user

GABATOR M
Gabapentin & Methylcobalamin Tablets

Read all of this leaflet carefully before you start using 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 9.4.

What is in this leaflet?

9.1 What GABATOR M is and what it is used for

GABATOR M is film coated tablet, contains Gabapentin & Methylcobalamin tablets and it is use for neuropathic pain in adults.

9.2 What you need to know before you use GABATOR M Do not take

Do not take GABATOR M

• if you are allergic (hypersensitive) to gabapentin, methylcobalamin or any of the other ingredients of this medicine.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Gabapentin. If you:

• suffer from kidney problems your doctor may prescribe a different dosing schedule

• are on haemodialysis (to remove waste products because of kidney failure), tell your doctor if you develop muscle pain and/or weakness.

• suffer with different types of seizures including absences.

• develop signs such as persistent stomach pain, feeling sick and being sick, contact your doctor immediately as these may be symptoms of acute pancreatitis (an inflamed pancreas)

• have nervous system disorders, respiratory disorders, or you are more than 65 years old, your doctor may prescribe you a different dosing regimen.

Cases of abuse and dependence have been reported for gabapentin from the post-marketing experience. Talk to your doctor if you have a history of abuse or dependence.

A small number of people being treated with anti-epileptics such as Gabapentin have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.

Important information about potentially serious reactions

A small number of people taking gabapentin get an allergic reaction or potentially serious skin reaction, which may develop into more serious problems if they are not treated. You need to know these symptoms to look out for while you are taking gabapentin.

Read the description of these symptoms in section 4 of this leaflet under 'Contact your doctor immediately if you experience any of the following symptoms after taking this medicine as they can be serious'

Talk to your doctor or pharmacist before taking Methylcobalamin tablets

The prologned use of larger doses of methylcobalamin is not recommended for patients whose occupation requires the handling of mercury or mercury compounds.

Use cautiously in patients with hypertension, cardiovascular and lung diseases. Cardiac arrhythmias secondary to hypokalaemia during initial therapy have been reported. Vitamin B12 should be given prophylactically only when there is a reasonable indication. Administration of methycobalamin doses greater than 10mcg daily, may produce a hematological response in patients with folate deficiency. It is important to monitor methylcobalamin concentrations in plasma and to obtain peripheral blood counts at intervals of 3 to 6 months to confirm that adequacy of therapy. Since refractoriness to therapy can develop at any time, evaluation must continue throughout the patient's life. Serum concentrations may be decreased by concurrent administration of oral contraceptives. Blood concentrations of methylcobalamin may be reduced if large doses of folate are taken continuous.

Children and adolescents

The dose depends on the body weight of your child. The treatment is started with a low initial dose which is gradually increased over a period of about 3 days. The usual dose to control epilepsy is 25-35mg per kg per day. It are not recommended for use in children below 6 years of age.

Other medicines and GABATOR M

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. In particular:

Gabapentin

• Tell your doctor (or pharmacist) if you are taking or have been recently taking any medicines for convulsions, sleeping disorders, depression, anxiety, or any other neurological or psychiatric problems.

• Medicines containing opioids such as morphine; if you are taking any medicines containing opioids (such as morphine), please tell your doctor or pharmacist as opioids may increase the effect of Gabapentin. In addition, combination of Gabapentin. With opioids may cause symptoms like sleepiness and/or decrease in breathing.

• Antacids containing aluminium and magnesium (used to reduce stomach acid): if taken at the same time, absorption of Gabapentin from the stomach may be reduced. It is therefore recommended that Gabapentin are taken at least two hours after taking an antacid.

Urine Tests

Gabapentin may interfere with urine tests. If you require a urine test, tell your doctor or hospital that you are taking Gabapentin.

Other medicines and Methycobalamin tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Tetracycline: Vitamin B12 should not be taken at the same time as the antibiotic Tetracycline because it interferes with the absorption and effectiveness of this medication. Vitamin B12 either alone or in combination with other B vitamins should be taken at different times of the day from tetracycline.

Chemotherapy Medications: Blood levels of Vitamin B12 may be reduced when taking chemotherapy medications (particularly methotrexate) for cancer.

Absorption of cobalamin is impaired by alcohol, vitamin B6 (pyridoxine) deficiency, cholestyramine, para-aminosalicylic acid colchicines, neomycin, the oral bigunades, metformin, histamine H2 receptor antagonists (clmetidine, ranitidine, etc.) phenformin and possibly potassium chloride. A number of anticonvulsants phenobarbitone, primidone, phenytoin, and ethylphenacemide can alter the metabolism of cobalamin in the cerebrospinal fluid and lead to neuropsychotic disturbances. Several substituted amide, lactone and lactum analogues of cyanocobalamin compete with binding sites on intrinsic factor and lead to depressed absorption of the vitamins. Nitrous oxide also interferes with cobalamin metabolism.

Pregnancy

• If you are pregnant or think you may be pregnant, you must tell your doctor straight away and discuss possible risks the medicine you are taking might pose to your unborn baby

• If you are planning to become pregnant you should discuss your treatment with your doctor as early as possible before you become pregnant

• You should not stop your treatment without discussing this with your doctor.

Gabapentin should not be taken during pregnancy, unless you are told otherwise by your doctor.

Effective contraception must be used by women of child-bearing potential.

There have been very few studies specifically looking at the use of gabapentin in pregnant women. More research is needed to better understand about the safety of use of gabapentin during pregnancy and whether it is associated with an increased risk of harm to the unborn child.

Some medicines used to treat epilepsy have reported an increased risk of harm to the developing baby, particularly when more than one seizure medication is taken at the same time. This means that where possible, your doctor should consider using one epilepsy medicine to control your epilepsy.

Fertility

There is no effect on fertility in animal studies. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding

Gabapentin is passed on through human milk. Because the effect on the baby is unknown, it is not recommended to breast-feed while using Gabapentin.

Driving and using machines

When taking Gabapentin you may become drowsy, dizzy or feel tired, especially at the start of treatment or after a dose increase. Make sure you are not affected before driving, operating machinery or taking part in other potentially hazardous activities.

9.3 How to use GABATOR M

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Gabapentin are usually taken three times a day (morning, afternoon and evening). Always swallow the tablet whole with plenty of water, with or without food. Your doctor will determine what dose is appropriate for you. If you are an elderly patient (over 65 years old), have kidney disease or are having haemodialysis, you should take Gabapentin as prescribed by your doctor. Continue taking Gabapentin until your doctor tells you to stop.

The average effective dose of methylcobalamin has been found to be 1500 mcg/day which is achieved by giving atleast 3 tablets a day.

If you take more GABATOR M than you should

If you or someone else accidentally takes too many or if you think a child has swallowed any, contact your doctor or go to your nearest hospital casualty department immediately. As Gabapentin may make you drowsy, it is recommended that you ask someone else to drive you to the doctor or hospital, or that you call an ambulance. Symptoms of an overdose are dizziness, double vision, slurred speech, drowsiness or tiredness, loss of consciousness and mild diarrhoea. Overdose of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

If you forget to take GABATOR M

Take the next dose on time. If you miss a dose, take it as soon as you remember, unless it

is time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking GABATOR M

Do not stop taking this medicine suddenly, as your symptoms may get worse. Your doctor will reduce the dose gradually, you may experience anxiety, difficulty sleeping, feeling sick, pain, sweating.

9.4 Possible Side Effects

Gabapentin

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Contact your doctor immediately if you experience any of the following symptoms after taking this medicine as they can be serious:

Rare (may affect up to 1 in 1,000 people):

• breathing problems, shallow breaths (respiratory depression), which if severe you may need emergency and intensive care to continue breathing normally.

Not known (frequency cannot be estimated from the available data):

• severe skin reactions that require immediate attention, swelling of the lips and face, skin rash and redness, and/or hair loss (these may be symptoms of a serious allergic reaction)

• persistent stomach pain, feeling sick and being sick as these may be symptoms of acute pancreatitis (an inflamed pancreas)

• suicidal thoughts

• anaphylaxis (serious, potentially life-threatening allergic reaction including difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment)

• Gabapentin may cause a serious or life-threatening allergic reaction that may affect your skin or other parts of your body such as your liver or blood cells. You may or may not have a rash when you get this type of reaction. It may cause you to be hospitalised or to stop Gabapentin.

Methycobalamin:

Generally well tolerated.

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 GABATOR M

Store Protected from light & moisture, at a temperature not exceeding 25°C.

Keep out of reach of children.

9.6 Contents of the pack and other information

GABATOR M contain active substance Gabapentin & Methycobalamin Tablets.

GABATOR M 100 is reddish brown coloured, round, biconvex, film coated tablets, plain

on both side. The excipients used are Microcrystalline Cellulose, Croscarmellose Sodium, Poloxamer 407, Pregelatinised Starch, Polyvinyl Pyrrolidone (K-30), Maize Starch, Purified water, Colloidal Silicon Dioxide, Magnesium Stearate, Isopropyl Alcohol, P.E.G.-400, H.P.M.C. (E5), Dichloromethane.

GABATOR M 300 is red coloured, round, biconvex, film coated tablets, Scored on one side and plain on other side. The excipients used are Colloidal Silicon Dioxide, Microcrystalline Cellulose, Maize Starch, Polyvinyl Pyrrolidone (K-30), Purified water, Magnesium Stearate, Sodium Starch Glycolate, Croscarmellose Sodium, Isopropyl Alcohol, Dichloromethane, H.P.M.C. (E5), P.E.G.-400, Purified Talc.

GABATOR M is packed in blister strip of 10 tablets

10 Details of manufacturer

Windlas Biotech Limited (Plant-2),
Khasra No. 141 to 143 & 145,
Mohabewala Industrial Area,
Dehradun-248110 (U.K.)
R.O.: 40/1, Mohabewala Indl. Area, Dehradun.

11 Details of permission or licence number with date

GABATOR M
55/UA/SC/P-2013 issued on 15.05.2022

12 Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ GABATOR M 100 and 300/AUG-2022/01/PI