Napo Gabapentin
Gabapentin Capsules 300 mg

COMPOSITION:
Each hard gelatin Capsule contains :
Gabapentin BP 300 mg
Excipients q.s.

DESCRIPTION:
Napo Gabapentin contains Gabapentin 300 mg. Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Antiepileptics
ATC code: N03AX12
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.

PHARMACOKINETICS:
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.

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.

Elimination
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 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.

INDICATION:
Epilepsy
Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalisation in adults and children aged 6 years and above.
Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalisation in adults and adolescents aged 12 years and above.
Treatment of peripheral neuropathic pain
Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

DOSAGE AND ADMINISTRATION:
Posology
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.

Dosing Chart-Initial Titration		
Day 1	Day 2	Day 3
300 mg once a day	300 mg two times a day	300 mg 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.
Epilepsy
Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.
Adults and adolescents:
In clinical trials, the effective dosing range was 900 to 3600mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300mg three times a day (TID) on Day 1. 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.
Dosages up to 4800mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.
Children aged 6 years and above:
The starting dose should range from 10 to 15mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6 years and older is 25 to 35mg/kg/day. Dosages up to 50mg/kg/day have been well tolerated in a long term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours.
It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicinal products without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicinal products.
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 (see Table 2). 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 capsules can be used to follow dosing recommendations for patients with renal insufficiency.
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.

Method of administration
Capsule for oral administration.

CONTRAINDICATION:
Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNING AND PRECAUTION FOR USE:
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 and the available data do not exclude the possibility of an increased risk for Gabapentin.
Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
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 refractory 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
Patients who require concomitant treatment with opioids should be carefully observed for signs of central nervous system (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 opioids should be reduced appropriately.
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.
Use in elderly patients (over 65 years of age)
No systematic studies in patients 65 years or older have been conducted with gabapentin. In one 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.
Gabapentin Accord-UK capsules contain lactose
Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose galactose malabsorption should not take this medicine.

INTERACTION WITH OTHER MEDICINE AND CONCOMITANT USE:
There are spontaneous and literature case reports of respiratory depression and/or sedation associated with gabapentin and opioid use. In some of these reports, the authors considered this a particular concern with the combination of gabapentin and opioids, especially in elderly patients.
In a study involving healthy volunteers (N=12), when a 60 mg 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.
Coadministration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.
Coadministration 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 coadministered with cimetidine is not expected to be of clinical importance.

FERTILITY, PREGNACY AND LACTATION
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 adequate 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 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.

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.

UNDESIRABLE EFFECTS:
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.
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: anaphylaxis, Hypersensitive syndrome, a systemic reaction with a variable presentation that can include fever, rash, hepatitis lymphadenopathy, eosinophilia and sometimes other signs and symptoms.
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
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 disorder
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.
Musculoskeletal, connective tissue and bone disorders
Common: arthralgia, myalgia, back pain, twitching
Not known: rhabdomyolysis, myoclonus
Renal and urinary disorders
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 and poisoning
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.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

OVERDOSE:
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.

INCOMPATIBILITY:
Not applicable.

SHELF LIFE:
3 years

PACKAGING:
10 tablets are packed in Alu-Alu Blister, such 1 blister is packed in a monocarton along with pack insert and, such 10 cartons are packed in outer carton.

STORAGE CONDITION:
Store in dry place below 30°C. Keep out of reach of children.

MANUFACTURED BY:
CIAN HEALTHCARE LTD.
(An ISO 9001 : 2015 & WHO GMP Certified Co.)
Kh. No. : 248, Village Sisona, Bhagwanpur,
Roorkee, Haridwar, Uttarakhand, India.