SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF DRUG PRODUCT:

Gabapentin Capsules 100 mg.

Gabapentin Capsules 300 mg.

Gabapentin Capsules 400 mg.

(TRADE) NAME OF PRODUCT: ONEGABA 100.

ONEGABA 300.

ONEGABA 400.

STRENGTH : 100 mg, 300 mg and 400 mg.

PHARMACEUTICAL DOSAGE FORM: Capsule.

QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Gabapentin Capsules 100 mg

Each capsule contains Gabapentin Ph.Eur. 100 mg.

Gabapentin Capsules 300 mg

Each capsule contains Gabapentin Ph.Eur. 300 mg.

Gabapentin Capsules 400 mg

Each capsule contains Gabapentin Ph.Eur. 400 mg.

PHARMACEUTICAL FORM:

Gabapentin Capsules 100 mg: White /White size '3' hard gelatin capsules imprinted with 'D' on white cap and '02' on white body with black edible ink filled with white to off white crystalline powder.

Gabapentin Capsules 300 mg: Yellow / Yellow size “1” hard gelatin capsules imprinted with 'D' on yellow cap and '03' on yellow body with black edible ink filled with white to off white crystalline powder.

Gabapentin Capsules 400 mg: Orange / Orange size '0' hard gelatin capsules imprinted with 'D' on orange cap and '04' on orange body with black edible ink filled with white to off white crystalline powder.

CLINICAL PARTICULARS:

Therapeutic indications

Epilepsy

Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adult and children aged 6 years and above.

Gabapentin is indicated as monotherapy in the treatments of partial seizures with and without secondary generalization 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 postherpetic neuralgia in adults.

Posology and method of administration

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
300 mg once a day	300 mg two time a day	300 mg three time 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:

The effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. Dosages up

to 4800 mg/day have been well tolerated. 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 15 mg/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 35 mg/kg/day. Dosages up to 50 mg/kg/day have been well tolerated. 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 900 mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

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 100 mg capsules 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 < 79 ml/min).

b. To be administered as 300 mg every other day.

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

Use in patients undergoing haemodialysis

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg, then 200 to 300 mg 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 300 mg dose following each 4-hour haemodialysis treatment is recommended.

Method of administration

For oral use.

Contraindications

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

Special warnings and precautions 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) occurs 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 behavior

Suicidal ideation and behaviour occurs in patients treated with anti-epileptic agents in several indications. 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 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). Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

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 depressionGabapentin 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.

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

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.

Interaction with other medicinal products and other forms of interaction

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.

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.

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 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 to< 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Infections and infestations

Very Common: Viral infection

Common: Pneumonia, respiratory infection, urinarytract infection, infection, otitis media

Blood and the lymphatic systemdisorders

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.

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

Unknown: 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, dysk inesia, 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, diarrhea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence

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, and acne

Not known: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia drug rash with eosinophilia and systemic symptoms

Musculoskeletal, connective tissue 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 occur 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 children. Additionally, in children, aggressive behaviour and hyperkinesias were reported commonly.

Pregnancy and Lactation:

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 practised 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

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

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.

Over dosage

Acute, life-threatening toxicity may not occur with gabapentin overdoses of up to 49 grams. 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, minimise 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 not usually required. However, in patients with severe renal impairment, haemodialysis may be indicated.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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 centers through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

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.

Pharmacokinetic properties

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 300 mg 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 2 μg/ml and 20 μg/ml, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

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

Pharmacokinetic parameter	300 mg (N = 7)		400 mg (N = 14)		800 mg (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)
$T_{1/2}$ (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}
$T_{1/2}$ = 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.

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.

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 $T_{1/2}$), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

PHARMACEUTICAL PARTICULARS

List of excipients

Maize Starch and Purified Talc.

Incompatibilities

None known.

Shelf life

24 moths

Special precautions for storage

Do not store above 30°C.

Nature and contents of container

Blister of 10 Capsules.

MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Ltd., India.

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MARKETING AUTHORISATION NUMBER

05796/07335/REN/2020

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Mar 19, 2021

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January 2018.