

## Data Sheet

### RANBAXY-GABAPENTIN

Gabapentin Capsules 100 mg, 300 mg and 400 mg

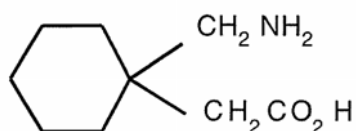
Gabapentin Tablets 600 mg and 800 mg

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#### Presentation

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Gabapentin (CAS 60142-96-3) is described as 1-(aminomethyl)-cyclohexane acetic acid with an empirical formula of C<sub>9</sub>H<sub>17</sub>NO<sub>2</sub> and a molecular weight of 171.24. The molecular structure of gabapentin is:



Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and both basic and acidic aqueous solutions.

**RANBAXY-GABAPENTIN 100 mg Capsules:** White, opaque coloured body and cap, size '4' hard gelatin capsules imprinted with G 100 on both cap and body in black edible ink containing white to off-white crystalline powder. Each capsule contains 100 mg of gabapentin.

**RANBAXY-GABAPENTIN 300 mg Capsules:** Ivory, opaque coloured body and cap, size '0' hard gelatin capsules imprinted with G 300 on both cap and body in black edible ink containing white to off-white crystalline powder. Each capsule contains 300 mg of gabapentin.

**RANBAXY-GABAPENTIN 400 mg Capsules:** Orange, opaque coloured body and cap, size '0 el' hard gelatin capsules imprinted with G 400 on both cap and body in black edible ink containing white to off-white crystalline powder. Each capsule contains 400 mg of gabapentin.

**RANBAXY-GABAPENTIN 600 mg tablets:** White to off-white, oval shaped, biconvex film coated tablets imprinted with "G600" in black ink on one side and plain on the other.

**RANBAXY-GABAPENTIN 800 mg tablets:** White to off-white, oval shaped, biconvex film coated tablets imprinted with "G800" in black ink on one side and plain on the other.

Do not halve tablets. Dose equivalence when tablets are divided has not been established.

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## Uses

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### **Actions**

The mechanism by which gabapentin exerts its anticonvulsant action is unknown. Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but its mechanism of action is different from that of several other medicines that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA pro-drugs. *In vitro* studies with radiolabelled gabapentin have characterised a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant activity of gabapentin and its structural derivatives. However, the identification and function of the gabapentin binding site remains to be elucidated. Gabapentin at relevant clinical concentrations does not bind to other common medicine or neurotransmitter receptors of the brain including GABA<sub>A</sub>, GABA<sub>B</sub>, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels *in vitro* and so differs from phenytoin and carbamazepine. Several test systems ordinarily used to assess activity at the NMDA receptor complex have been examined. Results are contradictory. Accordingly no general statement about the effects, if any, of gabapentin at the NMDA receptor can be made. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*. Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of the brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and shows efficacy in some, but not all, seizure models. These animal models included genetic models of seizures, and seizures induced by maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis.

### **Pharmacokinetics**

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolised in humans.

### **Absorption**

Gabapentin bioavailability is not dose proportional; ie. as dose is increased, bioavailability decreases. A 400 mg dose, for example, is about 25% less bioavailable than a 100 mg dose. Over the recommended dose range of 300 to 600 mg three times a day, however, the difference in bioavailability is not large, and bioavailability is about 60%. The bioavailability of the 800 mg dose was found to be approximately 35% in single and multiple dose studies. The absolute bioavailability of gabapentin following daily doses of 1200, 2400, 3600, and 4800 mg/day averaged 47%, 34%, 33%, and 27% respectively. Food has no effect on the rate and extent of absorption of gabapentin.

## Distribution

Gabapentin circulates largely unbound (< 3%) to plasma proteins. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is  $58 \pm 6$  L (Mean  $\pm$  SD). In patients with epilepsy, steady-state pre-dose (C<sub>min</sub>) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

## Elimination

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged medicine. Gabapentin is not appreciably metabolised in humans.

The elimination half-life of gabapentin is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed by haemodialysis.

Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see Dosage and Administration).

## Special Populations

*Patients with renal insufficiency:* Subjects with renal insufficiency (mean creatinine clearance ranging from 13 - 114 mL/min) were administered 400 mg oral dose of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (patients with creatinine clearance (CL<sub>cr</sub>) > 60 mL/min) to 52 hours (CL<sub>cr</sub> < 30 mL/min) and gabapentin renal clearance ranged from about 90 mL/min (CL<sub>cr</sub> > 60 mL/min) to about 10mL/min (CL<sub>cr</sub> < 30 mL/min). Gabapentin dosage should be adjusted in patients with compromised renal function (see Dosage and Administration).

*Patients on haemodialysis:* In a study in anuric patients, the elimination half-life of gabapentin on nondialysis day was about 132 hours; dialysis three times a week (4 hour duration) lowered the apparent half-life of gabapentin by about 60%, from 132 hours to 51 hours. Gabapentin dosage should be adjusted in patients undergoing haemodialysis (see Dosage and Administration).

*Elderly patients:* In a study examining the effect of age on the elimination of gabapentin, apparent oral clearance (CL/F) of gabapentin decreased as age increased, from about 225 mL/min in those under 30 years of age to about 125 mL/min in those over 70 years of age. Renal clearance also declined with age; however, the decline in the renal clearance of gabapentin can largely be explained by the decline in renal function. Reduction of gabapentin dose may be required in patients who have age related compromised renal function.

*Paediatric patients:* Gabapentin pharmacokinetics were determined in 24 healthy paediatric subjects between the ages of 4 and 12 years. In general, plasma gabapentin concentrations in children are similar to those in adults.

## Clinical Studies

The effectiveness of Gabapentin as adjunctive therapy was established in three multi-centre, placebo-controlled, double-blind, parallel-group clinical trials in 705 adults with refractory partial seizures. The patients enrolled had a history of at least 4 partial seizures per month in spite of receiving one or more antiepileptic drugs at therapeutic levels and were observed on their established antiepileptic drug regimen during a 12-week baseline period. In patients continuing to have at least 2 (or 4 in some studies) seizures per month, Gabapentin or placebo was then added on to the existing therapy during a 12-week treatment period. Effectiveness was assessed primarily on the basis of the percent of patients with a 50% or greater reduction in seizure frequency from baseline to treatment (the "responder rate") and a derived measure called response ratio, a measure of change defined as  $(T - B)/(T + B)$ , where B is the patient's baseline seizure frequency and T is the patient's seizure frequency during treatment. Response ratio is distributed within the range -1 to +1. A zero value indicates no change while complete elimination of seizures would give a value of -1. Increased seizure rates would give positive values. A response ratio of -0.33 corresponds to a 50% reduction in seizure frequency. The results given below are for all partial seizures in the intent-to-treat (all patients who received any doses of treatment) population in each study, unless otherwise indicated.

One study compared Gabapentin 1200 mg/day T.I.D. with placebo. Responder rate was 23% (14/61) in the Gabapentin group and 9% (6/66) in the placebo group; the difference between groups was statistically significant. Response ratio was also better in the Gabapentin group (-0.199) than in the placebo group (-0.044), a difference that also achieved statistical significance.

A second study compared primarily 1200 mg/day T.I.D. Gabapentin (N=101) with placebo (N=98). Additional Gabapentin dosage groups (600 mg/day, N=53; 1800 mg/day, N=54) were also studied for information regarding dose response. Responder rate was higher in the Gabapentin 1200 mg/day group (16%) than in the placebo group (8%), but the difference was not statistically significant. The responder rate at 600 mg (17%) was also not significantly higher than in the placebo, but the responder rate in the 1800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the Gabapentin 1200 mg/day group (-0.103) than in the placebo group (-0.022); but this difference was also not statistically significant ( $p = 0.224$ ). A better response was seen in the Gabapentin 600 mg/day group (-0.105) and 1800 mg/day group (-0.222) than in the 1200 mg/day group, with the 1800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared Gabapentin 900 mg/day given as three divided doses (N = 111) and placebo (N = 109). An additional Gabapentin 1200 mg/day dosage group (N = 52) provided dose-response data. A statistically significant difference in responder rate was seen in the Gabapentin 900 mg/day group (22%) compared to that in the placebo group (10%). Response ratio was also statistically significantly superior in the Gabapentin 900 mg/day group (-0.119)

compared to that in the placebo group (-0.027), as was response ratio in 1200 mg/day Gabapentin (-0.184) compared to placebo.

A one week, prospective, multi-centre, randomised, double-blind, placebo lead-in, parallel-group study compared the tolerability of Gabapentin administered as an initial dosage of 900 mg/day versus a dosage titrated to 900 mg/day over three days (ie. 300 mg on Day 1, 600 mg on Day 2, 900 mg on Day 3). 781 patients (titrated = 383, nontitrated = 388) involved in the study had partial seizures which were not adequately controlled with one or two other antiepileptic drugs. For the MITT population, on both the first day of active medication, and all 5 days of active medication, there were no clinically meaningful treatment group differences in the incidences of fatigue, ataxia, and somnolence (ie. the upper 95% confidence limit for the difference < 7.5%). Only the difference in dizziness exceeded this upper confidence limit (upper confidence limit = 10.7% for the first day and 11.3% for all 5 days), with the nontitrated group reporting the higher incidence, however, it did not lead to increased discontinuation in this group.

The safety and efficacy of Gabapentin administered as adjunctive therapy for the treatment of partial seizures in pAEMiatric patients aged 3 to 12 years were assessed in two randomised, double-blind, parallel-group, placebo-controlled, multicentre clinical studies. The studies were conducted in 247 children who had refractory partial seizures and were receiving 1 to 3 standard antiepileptic medicines. After a 6-week baseline phase, during which patients received their prescribed antiepileptic medicines, there was a 12-week double-blind treatment phase. Patients who had experienced a minimum of 4 seizures during baseline were randomised and had either Gabapentin (25 to 35 mg/kg/day) or placebo added to their baseline AEMs. The primary analysis of RRatio (MITT population) demonstrated that Gabapentin was significantly better than placebo in controlling partial seizures ( $p = 0.04$ ). Results for the ITT population did not show a significant difference in RRatio between the treatment groups. Further analysis using rank-transformed data was performed as the data showed evidence of non-normality of distribution. Results of this analysis showed that mean RRatio was significantly lower (better) for the gabapentin treatment group than for the placebo group in both the MITT ( $p = 0.01$ ) and ITT ( $p = 0.03$ ) populations.

The efficacy and safety of Gabapentin for the treatment of neuropathic pain in adults over 18 years of age were assessed in two randomised, double-blind, parallel-group, placebo-controlled, multicentre studies. One study examined the efficacy and safety of Gabapentin in the treatment of painful diabetic peripheral neuropathy and the other study was conducted in patients with post-herpetic neuralgia. The studies were of a similar design. Following a baseline screening week and randomisation, Gabapentin was titrated from 900 mg/day to 1800 mg, 2400 and 3600 mg/day divided into three times a day dosing consecutively over the first four weeks of the study. Patients were then maintained at the maximum dose that was tolerated for the remaining four weeks. The primary efficacy measure used in both studies was change from baseline to the final week in mean pain score obtained from daily pain diaries (pain was measured using an 11-point Likert scale). Several secondary

outcomes were also assessed including: the Short-Form McGill Pain Questionnaire (SF-MPQ) (sensory, affective and total pain scores), SF-MPQ visual analogue scale (VAS) and present pain intensity scale (PPI), mean sleep interference score, Patient and Clinical Global Impression of Change (PGIC and CGIC), and the quality of life measures SF-36 Quality of Life Questionnaire (QOL) and Profile of Mood States (POMS).

Results from both studies demonstrated that Gabapentin provided statistically significantly greater improvement in relief of neuropathic pain than placebo. In patients with painful diabetic peripheral neuropathy, mean pain score decreased by 2.6 in patients receiving Gabapentin and 1.4 in patients receiving placebo ( $p < 0.001$ ). In the post-herpetic neuralgia study, mean pain score decreased by 2.1 in patients receiving Gabapentin and 0.5 in patients receiving placebo ( $p < 0.001$ ). Gabapentin was significantly better than placebo in controlling pain from week two of both studies ( $p < 0.001$ ). Sleep interference scores, Short-Form McGill sensory, affective and total pain scores, VAS and PPI scale as well as PGIC, CGIC and some of the quality of life measures showed significant differences in favour of Gabapentin.

### ***Indications***

RANBAXY-GABAPENTIN is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures, in adults and children age three years and above who have not achieved adequate control with standard anti-epileptic medicines (see Dosage and Administration).

RANBAXY-GABAPENTIN is indicated for the treatment of neuropathic pain (see Dosage and Administration).

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## **Dosage and Administration**

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Do not halve tablets. Dose equivalence when tablets are divided has not been established.

### ***Epilepsy:***

#### **Adults and Children Over 12 years of Age:**

Initiation of treatment should be as add-on therapy. Gabapentin can be given orally with or without food.

In controlled clinical trials, the effective dose range was 900 to 1800 mg/day given in divided doses (three times a day).

Therapy may be initiated by administering 300 mg three times a day on Day 1 or by titrating the dose as described: Titration to an effective dose can take place rapidly, over a few days, by giving 300 mg gabapentin on Day 1, 300 mg gabapentin twice a day on Day 2, and 300 mg gabapentin three times a day on Day 3. Titration may be preferable for patients with renal impairment, patients with encephalopathy, patients on more than 2 other anti-epileptic medicines and patients with multiple other medical problems.

To minimise potential side effects, especially somnolence, dizziness, fatigue and ataxia, the first dose on Day 1 may be administered at bedtime. If necessary, the dose may be increased using 300 or 400 mg capsules or 800 mg tablets three times a day up to 2400 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term open-label clinical studies. The maximum time between doses in the three times a day (TID) schedule should not exceed 12 hours to prevent breakthrough convulsions.

### **Children Aged 3 to 12 Years of Age:**

The effective dose of gabapentin is 25 to 35 mg/kg/day given in equally divided doses (3 times a day) as described in Table 1. Initial titration to an effective dose can take place over 3 days by giving 10 mg/kg/day on Day 1, 20 mg/kg/day on Day 2, and 30 mg/kg/day on Day 3. Thereafter, the dose can be increased in three equally divided doses up to a maximum dose of 35 mg/kg/day. Dosages up to 40 to 50 mg/kg/day have been well tolerated in a long-term clinical study. Doses of 60 mg/kg/day have also been administered to a small number of children.

**Table 1: Dosage of Gabapentin in Paediatric Patients Age 3-12 Years**

<b>Weight Range (kg)</b>	<b>Daily Dose (mg/day)</b>
17 - 25	600
26 - 36	900
37 - 50	1200
51 - 72	1800

Unlike other agents in this class, it is not necessary to monitor gabapentin plasma concentrations to optimise gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicines without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicines. If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of one week.

### ***Neuropathic Pain***

#### **Adults (over 18 years of age):**

The starting dose is 900 mg/day given as three equally divided doses, and titrated if necessary, based on response, up to a maximum dose of 3600 mg/day.

#### ***Dosage adjustment in Impaired Renal function for Patients with Neuropathic Pain or Epilepsy:***

Dosage adjustment is recommended in patients with compromised renal function and/or those undergoing haemodialysis as described in Table 2.

**Table 2: Dosage of Gabapentin in Adults Based on Renal Function**

<b>Creatinine Clearance (mL/min)</b>	<b>Total Daily Dose<sup>a</sup> (mg/day)</b>
≥ 80	900-3600
50-79	600-1800
30-49	300-900
15-29	150 <sup>b</sup> -600
<15	150 <sup>b</sup> -300

<sup>a</sup> Total daily dose should be administered as a divided tid regimen. Doses used to treat patients with normal renal function (creatinine clearance > 80 ml/min) range from 900 to 3600 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 ml/min).

<sup>b</sup> To be administered as 300 mg every other day.

### ***Dosage Adjustment in Patients Undergoing Haemodialysis:***

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

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## **Contraindications**

RANBAXY-GABAPENTIN is contraindicated in patients who have demonstrated hypersensitivity to gabapentin or the inactive ingredients in the capsules.

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## **Warnings and Precautions**

### ***General***

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus. When in the judgement of the clinician there is a need for dose reduction, discontinuation, or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of one week.

Gabapentin is not generally considered effective in the treatment of absence seizures and may exacerbate these seizures in some patients. Consequently, RANBAXY-GABAPENTIN should be used with caution in patients who have mixed seizure disorders that include absence seizures.

Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of RANBAXY-GABAPENTIN or morphine should be reduced appropriately (see Interactions).

### ***Suicidal Behaviour and Ideation***

Antiepileptic medicines (AEM), including gabapentin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AEM for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behaviour, and/or any unusual changes in mood or behaviour.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEMs showed that patients randomised to one of the AEMs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behaviour or ideation among 27,863 AEM-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behaviour for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behaviour with AEMs was observed as early as one week after starting drug treatment with AEMs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behaviour beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behaviour was generally consistent among drugs in the data analysed. The finding of increased risk with AEMs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEMs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analysed. Table 3 shows absolute and relative risk by indication for all evaluated AEMs.

**TABLE 3 Risk by indication for antiepileptic drugs in the pooled analysis**

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behaviour was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing gabapentin or any other AEM must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEMs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behaviour. Should suicidal thoughts and behaviour emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEMs increase the risk of suicidal thoughts and behaviour and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behaviour, or the emergence of suicidal thoughts, behaviour, or thoughts about self-harm. Behaviours of concern should be reported immediately to the treating doctor.

### ***Information for Patients***

To assure safe and effective use of RANBAXY-GABAPENTIN, the following information and instructions should be given to patients:

1. Inform your physician about any prescription or non-prescription medications, alcohol, or medicines you are now taking or plan to take during your treatment with RANBAXY-GABAPENTIN.
2. No teratogenic effects have been found in animals. However, the risk to the human foetus cannot be dismissed. Therefore you should inform your physician if you are pregnant, or if you are planning to become pregnant, or if you become pregnant while you are taking RANBAXY-GABAPENTIN.
3. Gabapentin is excreted in human milk, and the effect on the nursing infant is unknown. You should inform your physician if you are breast feeding an infant (see Use in Pregnancy and Use in Lactation).
4. Gabapentin may impair your ability to drive a car or operate potentially dangerous machinery. Until it is known that this medication does not affect your ability to engage in these activities, do not drive a car or operate potentially dangerous machinery.
5. You should not allow more than 12 hours between RANBAXY-GABAPENTIN doses to prevent breakthrough convulsions. If you have missed a dose by not more than 4 hours, take the dose as soon as you remember. However, if you have missed a dose by more than 4 hours, you should skip the dose and continue taking following doses as usual.

### ***Carcinogenesis, Mutagenesis, Impairment of Fertility***

Gabapentin was given in the diet to mice at 200, 600 and 2000 mg/kg/day and to rats at 250, 1000 and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell adenoma and carcinoma was found only in male rats at the highest dose. Peak plasma concentrations and areas under the concentration time curve in rats at 2000 mg/kg/day are 14 times higher than plasma concentrations in humans given

the recommended maximum tolerated dose of 2400 mg/day. The pancreatic acinar cell tumours in male rats are low-grade malignancies, did not metastasise 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 human is unclear.

There is no evidence that gabapentin has 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.

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg/day.

### ***Use in Pregnancy: Category B1***

The risk of having an abnormal child as a result of antiepileptic medication is far outweighed by the dangers to the mother and foetus of uncontrolled epilepsy.

It is recommended that:

- women on antiepileptic medicines (AEMs) receive pre-pregnancy counselling with regard to the risk of foetal abnormalities;
- AEMs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication;
- folic acid supplementation (5 mg) should be commenced four weeks prior to and continue for twelve weeks after conception;
- Specialist pre-natal diagnosis including detailed mid-trimester ultrasound should be offered.

Reproduction studies in mice at doses up to 3000 mg/kg/day and in rats at doses up to 2000 mg/kg/day revealed no evidence of impaired fertility or harm to the foetus due to gabapentin administration. In these studies, exposure to gabapentin (based on areas under the concentration time curve) was up to 5 times higher in the mouse, and up to 14 times higher in the rat, than in humans at the recommended maximum tolerated dose of 2400 mg/day. In rabbits given 60, 300 or 1500 mg/kg/day gabapentin during the period of organogenesis, maternal toxicity and abortion were observed at the high dose, but at the low and mid doses, no evidence of impaired fertility or harm to the foetus was observed. There are, however, no adequate and well-controlled studies in pregnant women. Therefore, this medicine should be used during pregnancy only if clearly needed.

### ***Use in Lactation***

Gabapentin is excreted in human milk. In a peri-postnatal study in rats at doses of 500, 1000 and 2000 mg/kg/day, there was a dose related increase in the incidence of hydronephrosis in 21 day-old pups. Because the effect on the nursing infant is unknown, and because of the potential for serious adverse reactions in nursing infants from gabapentin, a decision should be made whether to discontinue nursing or to discontinue the medicine, taking into account the importance of the medicine to the mother. Gabapentin should be used in nursing mothers only if the benefits clearly outweigh the risks.

### ***Effects on Ability to Drive and Use Machines***

Patients should be advised not to drive a car or operate potentially dangerous machinery until it is known that this medication does not affect their ability to engage in these activities.

### ***Use in Children***

Epilepsy: Safety and effectiveness in children below the age of 3 years have not been established.

Neuropathic Pain: Safety and effectiveness in children below the age of 18 years have not been established.

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## **Adverse Effects**

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### ***Epilepsy:***

#### **Adults and children over 12 years of age:**

Gabapentin has been evaluated for safety in approximately 2000 subjects and patients and was well tolerated. Of these, 543 patients participated in controlled clinical trials.

The most commonly observed adverse events associated with the use of gabapentin in combination with other antiepileptic medicines, not seen in an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue, and nystagmus.

Approximately 7% of the 2074 individuals who received gabapentin in the premarketing clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were somnolence, ataxia, fatigue, nausea and/or vomiting, and dizziness.

#### **Incidence in Controlled Clinical Trials**

Table 4 lists treatment-emergent signs and symptoms that occurred in at least 1% of gabapentin-treated patients with epilepsy participating in gabapentin placebo-controlled trials. In these studies, either gabapentin or placebo was added to the patient's current antiepileptic medicine therapy. Adverse events were usually mild to moderate in intensity.

**Table 4: Summary of Treatment-Emergent Signs and Symptoms in  $\geq 1\%$  of Gabapentin-Treated Patients in Adjunctive Therapy Placebo-Controlled Studies**

<b>Body System/Adverse Event</b>	<b>Gabapentin<sup>a</sup> N=543</b>		<b>Placebo<sup>a</sup> N=378</b>	
<b>Body as a Whole</b>				
Abdominal Pain	10	1.8	9	2.4
Back Pain	10	1.8	2	0.5
Fatigue	60	11.0	19	5.0
Fever	7	1.3	5	1.3
Headache	44	8.1	34	9.0
Viral Infection	7	1.3	8	2.1
Peripheral Oedema	9	1.7	2	0.5
Weight Increase	16	2.9	6	1.6
<b>Cardiovascular</b>				
Vasodilation	6	1.1	1	0.3
<b>Digestive System</b>				
Constipation	8	1.5	3	0.8
Dental Abnormalities	8	1.5	1	0.3
Diarrhoea	7	1.3	8	2.1
Dyspepsia	12	2.2	2	0.5
Increased Appetite	6	1.1	3	0.8
Mouth or Throat Dry	9	1.7	2	0.5
Nausea and/or vomiting	33	6.1	27	7.1
<b>Haematologic and Lymphatic</b>				
Leucopenia	6	1.1	2	0.5
WBC Decreased	6	1.1	2	0.5
<b>Musculoskeletal System</b>				
Fracture	6	1.1	3	0.8
Myalgia	11	2.0	7	1.9
<b>Nervous System</b>				
Amnesia	12	2.2	0	0.0
Ataxia	68	12.5	21	5.6
Confusion	9	1.7	7	1.9
Coordination Abnormal	6	1.1	1	0.3
Depression	10	1.8	7	1.8
Dizziness	93	17.1	26	6.9
Dysarthria	13	2.4	2	0.5
Emotional Lability	6	1.1	5	1.3
Insomnia	6	1.1	7	1.9
Nervousness	13	2.4	7	1.9
Nystagmus	45	8.3	15	4.0
Somnolence	105	19.3	33	8.7

Thinking Abnormal	9	1.7	5	1.3
Tremor	37	6.8	12	3.2
Twitching	7	1.3	2	0.5
<b>Respiratory System</b>				
Coughing	10	1.8	5	1.3
Pharyngitis	15	2.8	6	1.6
Rhinitis	22	4.1	14	3.7
<b>Skin and Appendages</b>				
Abrasion	7	1.3	0	0.0
Acne	6	1.1	5	1.3
Pruritus	7	1.3	2	0.5
Rash	8	1.5	6	1.6
<b>Special Senses</b>				
Amblyopia	23	4.2	4	1.1
Diplopia	32	5.9	7	1.9
<b>Urogenital System</b>				
Impotence	8	1.5	4	1.1

<sup>a</sup> Includes concomitant antiepileptic medicine therapy

### ***Other Adverse Events Observed During All Clinical Studies***

Those events that occurred in at least 1% of the study participants with epilepsy who received gabapentin as adjunctive therapy in any clinical study and that are not described in the previous section as frequently occurring treatment-emergent signs and symptoms during placebo-controlled studies are summarised below.

**Body as A Whole:** asthenia, malaise, facial oedema

**Cardiovascular System:** hypertension

**Digestive System:** flatulence, anorexia, gingivitis

**Haematological and Lymphatic Systems:** purpura most often described as bruises resulting from physical trauma

**Musculoskeletal System:** arthralgia

**Nervous System:** vertigo, hyperkinesia, increased, decreased or absent reflexes, paraesthesia, anxiety, hostility

**Respiratory System:** pneumonia

**Urogenital System:** urinary tract infection

**Special Senses:** abnormal vision

### Children From 3 to 12 Years of Age:

The most commonly observed adverse events reported with the use of gabapentin in combination with other antiepileptic medicines in children 3 to 12 years of age, not seen in equal frequency among placebo-treated patients, were viral infection, fever, nausea and/or vomiting, and somnolence.

Approximately 8% of the 292 children age 3 to 12 years who received gabapentin in pre-approval clinical trials discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal in children were somnolence (1.4%), hyperkinesia (1.0%), and hostility (1.0%).

**Table 5: Treatment-Emergent Adverse Event Incidence in Children Age 3 to 12 Years in Controlled Add-On Trials (Events in at least 2% of Gabapentin patients and numerically more frequent than in the placebo group)**

<b>Body System/Adverse Event</b>	<b>Gabapentin<sup>a</sup> N=119 %</b>	<b>Placebo<sup>a</sup> N=128 %</b>
<b>Body as a Whole</b>		
Viral Infection	10.9	3.1
Fever	10.1	3.1
Weight Increase	3.4	0.8
Fatigue	3.4	1.6
<b>Digestive System</b>		
Nausea and/or vomiting	8.4	7.0
<b>Nervous System</b>		
Somnolence	8.4	4.7
Hostility	7.6	2.3
Emotional Lability	4.2	1.6
Dizziness	2.5	1.6
Hyperkinesia	2.5	0.8
<b>Respiratory System</b>		
Bronchitis	3.4	0.8
Respiratory Infection	2.5	0.8

<sup>a</sup> Includes concomitant antiepileptic medicine therapy

Other events in more than 2% of children but equally or more frequent in the placebo group included: pharyngitis, upper respiratory infection, headache, rhinitis, convulsions, diarrhoea, anorexia, coughing, and otitis media.

Adverse events occurring during clinical trials in children treated with gabapentin that were not reported in adjunctive therapy trials in adults are:

**Body as a whole:** dehydration, infectious mononucleosis

**Digestive System:** hepatitis, oral moniliasis

**Haemic and Lymphatic System:** coagulation defect

**Nervous System:** aura disappeared, occipital neuralgia

**Psychobiologic Function:** sleepwalking

**Respiratory System:** pseudo-croup, hoarseness.

### **Neuropathic Pain**

#### **Adults Over 18 Years of Age**

The most commonly observed adverse events reported with the use of gabapentin in adults over 18 years of age with neuropathic pain, seen in at least twice the frequency among placebo-treated patients, were dry mouth, peripheral oedema, weight gain, abnormal gait, amnesia, ataxia, confusion, dizziness, hypoaesthesia, somnolence, thinking abnormal, vertigo, rash, and amblyopia.

Of the 821 adults who received gabapentin, in the painful diabetic peripheral neuropathy and post-herpetic neuralgia trials, 13.2% discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were dizziness (4.4%), somnolence (2.9%), and nausea (1.3%).

Of the two treatment groups, gabapentin and placebo, the only adverse event observed in both groups with an equal percentage greater than 2% was flu syndrome.

**Table 6: Summary of Treatment-Emergent Signs and Symptoms in  $\geq 1\%$  of Gabapentin-Treated Patients in Neuropathic Pain Placebo-Controlled Studies**

<b>Body System/Adverse Event</b>	<b>Gabapentin N=821</b>		<b>Placebo N=537</b>	
	<b>N of Pts</b>	<b>(%)</b>	<b>N of Pts</b>	<b>(%)</b>
<b>Body as a Whole</b>				
Abdominal Pain	23	2.8	17	3.2
Accidental Injury	32	3.9	17	3.2
Asthenia	41	5.0	25	4.7
Back Pain	19	2.3	4	1.5
Flu Syndrome	21	2.6	14	2.6
Headache	45	5.5	33	6.1
Infection	38	4.6	40	7.4
Pain	30	3.7	36	6.7
<b>Digestive System</b>				
Constipation	19	2.3	9	1.7

Diarrhoea	46	5.6	24	4.5
Dry Mouth	27	3.3	5	0.9
Dyspepsia	16	1.9	10	1.9
Flatulence	14	1.7	6	1.1
Nausea	45	5.5	29	5.4
Vomiting	16	1.9	13	2.4
<b>Metabolic and Nutritional</b>	44	5.4	14	2.6
Peripheral Oedema	14	1.7	0	0.0
Weight Gain				
<b>Nervous System</b>				
Abnormal Gait	9	1.1	0	0.0
Amnesia	15	1.8	3	0.6
Ataxia	19	2.3	0	0.0
Confusion	15	1.8	5	0.9
Dizziness	173	21.1	35	6.5
Hypoaesthesia	11	1.3	3	0.6
Somnolence	132	16.1	27	5.0
Thinking Abnormal	12	1.5	0	0.0
Tremor	9	1.1	6	1.1
Vertigo	8	1.0	2	0.4
<b>Respiratory System</b>				
Dyspnoea	9	1.1	3	0.6
Pharyngitis	15	1.8	7	1.3
<b>Skin and Appendages</b>				
Rash	14	1.7	4	0.7
<b>Special Senses</b>				
Amblyopia	15	1.8	2	0.4

### ***Post-marketing Experience***

The following adverse events have been reported in patients receiving gabapentin post-marketing, however, the data are insufficient to support an estimate of their incidence or to establish causation.

Sudden, unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established. Additional post-marketing adverse events reported include acute kidney failure, renal impairment, allergic reaction including urticaria, alopecia, anaemia, angioedema, convulsions, depersonalisation, urinary incontinence, pancreatitis, erythema multiforme, \*hypersensitivity including systemic reactions, jaundice, movement disorders such as choreoathetosis, dyskinesia and dystonia, speech disorder, sexual dysfunction, palpitation, tachycardia, Stevens-Johnson syndrome, thrombocytopenia, tinnitus, blood glucose fluctuations in patients with diabetes, breast hypertrophy, gynaecomastia,

cardiac arrest, chest pain, abnormal liver function and symptoms of psychosis such as delusions, hallucinations, and abnormal thinking.

Generalised oedema, hepatitis, hypotension, neuropathy/peripheral neuropathy and syncope have been rarely reported.

Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, pain, and sweating.

Sensory neuropathy has also been reported in a single patient being treated with gabapentin.

Some cases of hypomania have been reported after commencement of gabapentin. In each case, other anticonvulsants had been used concurrently, and symptoms of hypomania resolved following a reduction in dosage or cessation of the medicine.

\*The following adverse effects have not been identified as specific to gabapentin. However, antiepileptic medicines have been associated with an increased risk of suicidal behaviour, suicidal ideation and emergence or worsening of existing depression.

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## **Interactions**

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### **Effects on Laboratory Tests**

False positive readings were reported with the Ames N-Multistix SG® dipstick test when gabapentin was added to other anticonvulsant drugs. To determine urinary protein, the more specific sulfosalicylic acid precipitation procedure is recommended.

### **Interactions with Other Medicines**

In pharmacokinetic studies, no interactions were observed between gabapentin and phenobarbital (number of subjects, N=12), phenytoin (N=8), valproic acid (N=17), or carbamazepine (N=12).

Gabapentin did not influence the steady-state pharmacokinetics of norethindrone and ethinyl estradiol when administered concomitantly with an oral contraceptive containing these two medicines (N=13).

Coadministration of gabapentin with antacid reduced gabapentin bioavailability by about 20% (N=16).

In the presence of cimetidine at 300 mg four times a day, the mean apparent oral clearance of gabapentin fell by 14% and creatinine clearance by 10% (N=12). Thus cimetidine appeared to alter the renal excretion of both gabapentin and creatinine, an endogenous marker of renal function. Renal excretion of gabapentin was unaltered by probenecid, a blocker of renal tubular secretion.

**Morphine:** A literature article reported that when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule (N = 12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see Warnings and Precautions). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin two hours after morphine. The magnitude of interaction at other doses is not known.

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## Overdosage

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An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation. No deaths or medicine-related toxic effects were seen in monkeys which received gabapentin doses up to 1250 mg/kg orally.

## Symptoms

Symptoms of an overdose included somnolence, ataxia, dizziness, double vision, nystagmus, slurred speech, drowsiness, lethargy, mild hypotension and gastrointestinal symptoms including diarrhoea. Gabapentin overdose alone has not been reported to produce significant cardiotoxicity.

Overdoses as high as 108 g have been reported with full recovery following symptomatic therapy. Reduced absorption of gabapentin at higher doses may limit medication absorption at the time of overdosing and, hence, minimise toxicity from overdoses.

## Management

There is no specific antidote for gabapentin, so treatment of overdose is symptomatic. The patient should be monitored closely and given supportive care where necessary to maintain vital functions.

Overdoses may involve other concurrent medications and should be treated accordingly.

Activated charcoal may reduce absorption of the medication if given within one hour after ingestion. In patients who are not fully conscious or have an impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected.

Gabapentin can be removed by haemodialysis. Although haemodialysis has not been performed in the few overdose cases reported, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Ipecac-induced emesis is not recommended because of the potential for CNS depression.

Contact the Poisons Information Centre for advice on the management of overdose.

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## Pharmaceutical Precautions

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### ***Special Precautions for Storage***

Store capsules and tablets at temperatures below 25°C

### ***Shelf Life***

Capsules and tablets: 2 years

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## Medicine Classification

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Prescription medicine

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## Package Quantities

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RANBAXY-GABAPENTIN 100 mg, 300 mg and 400 mg capsules are available in bottle packs of 100 and 500.

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## Further Information

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### **List of Excipients:**

The excipients in **RANBAXY-GABAPENTIN 100 mg capsules** are mannitol, maize starch, talc, magnesium stearate. The capsule cap and body contains titanium dioxide and gelatin.

The excipients in **RANBAXY-GABAPENTIN 300 mg capsules** are mannitol, maize starch, talc, magnesium stearate. The capsule cap and body contains yellow iron oxide, titanium dioxide and gelatin.

The excipients in **RANBAXY-GABAPENTIN 400 mg capsules** are mannitol, maize starch, talc, magnesium stearate. The capsule cap and body contains red and yellow iron oxide, titanium dioxide and gelatin.

The printing inks of the 100 mg, 300 mg and 400 mg capsules contains: shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide, potassium hydroxide and purified water. The proprietary ingredient numbers are (TT70-09-2-2) and (TT70-09-2-3).

**RANBAXY GABAPENTIN 600 mg and 800 mg tablets** also contain the following inactive ingredients: hydroxypropyl cellulose, mannitol, crospovidone, talc, magnesium stearate, poloxamer 407. The coating ingredient is Opadry 20A59015 (Proprietary ingredient number TT70-03-6-5) and the printing ink is Opacode S-1-17734 (black [Proprietary ingredient number TT70-06-3-5]).

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**Name and Address**

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**Date of Preparation**

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31 March 2011