NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Gabapentin 100 mg, 300 mg and 400 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg capsule contains 100 mg of gabapentin.
Each 300 mg capsule contains 300 mg of gabapentin.
Each 400 mg capsule contains 400 mg of gabapentin.

Excipient(s) with known effect:
Each 100 mg capsule contains 16.83 mg lactose (as monohydrate).
Each 300 mg capsule contains 50.50mg lactose (as monohydrate).
Each 400 mg capsule contains 67.33 mg lactose (as monohydrate).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Capsules

100 mg capsule: White hard capsule, imprinted "100"
300 mg capsule: Yellow hard capsule, imprinted with "300"
400 mg capsule: Orange hard capsule, imprinted with "400".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gabapentin is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures, in adults and children age 3 years and above who have not achieved adequate control with standard anti-epileptic drugs (see **section 4.2**).

Gabapentin is indicated for the treatment of neuropathic pain (see **section 4.2**).

4.2 Dose and method of administration

Epilepsy

Adults and Children Older than 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 mg/day to 1800 mg/day given in divided doses (three times a day).

Therapy may be initiated by administering 300 mg of gabapentin three times a day on Day 1 or by titrating the dose as described below.

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 medications 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 mg or 400 mg capsules 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 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 mg/kg/day to 35 mg/kg/day given in 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 mg/kg/day 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

Weight Range (kg)	**Daily Dose (mg/day)**
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 anti-epileptic drugs without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other anti-epileptic drugs. If gabapentin is discontinued and/or an alternate anticonvulsant medication is added to the therapy, this should be done gradually over a minimum of 1 week.

Neuropathic Pain

Adults Older than 18 Years of Age

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

Dose Adjustment in Impaired Renal Function in Patients With Neuropathic Pain Or Epilepsy

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

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	150[b]-300

[a] Total daily dose should be administered as a divided three times a day regimen. Doses used to treat patients with normal renal function (creatinine clearance ≥80 mL/min) range from 900 mg/day to 3600 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance <79 mL/min).
[b] 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 mg to 400 mg is recommended, and then 200 mg to 300 mg of gabapentin following each 4 hours of haemodialysis.

Elderly (>65 years)

No dosage adjustment is necessary for elderly patients unless their renal function is compromised (see Table 2).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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 confusion, loss of consciousness and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Respiratory Depression

Patients who require concomitant treatment with opioids may experience increases in gabapentin concentrations. Patients who require concomitant treatment with CNS depressants, including opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or concomitant treatment with CNS depressants including opioids should be reduced appropriately (see **section**

4.5).

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

Suicidal Behaviour and Ideation

Anti-epileptic drugs (AED), including gabapentin, increase the risk of suicidal thoughts or behaviour in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or 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 AEDs showed that patients randomised to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behaviour compared to patients randomised 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 AED-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 AEDs was observed as early as one week after starting drug treatment with AEDs 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 AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs 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 AEDs.

Table 3: Risk by Indication for Anti-epileptic 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 AED must balance this risk with the

risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and 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 AEDs 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.

Drug Rash with Eosinophilia and Systemic Symptoms

Severe, life-threatening, systemic hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking anti-epileptic 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 aetiology 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.

Abuse and Dependence

Post-marketing cases of abuse and dependence have been reported with gabapentin. As with other CNS drugs, patients should be carefully evaluated for a history of drug abuse and/or psychiatric disorders.

Caution should be applied when considering gabapentin use in patients with current substance abuse or a history of substance abuse, who may be at higher risk for gabapentin abuse.
Patients treated with gabapentin should be monitored for signs and symptoms of gabapentin abuse or dependence, such as the development of tolerance, dose escalation and drug-seeking behaviour.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed in some patients. Withdrawal symptoms may occur shortly after the discontinuation, usually within 48 hours. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise.

Women of childbearing potential/Contraception

Gabapentin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Gabapentin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Women of childbearing potential must use effective contraception during treatment (see Section 4.6 Fertility, pregnancy and lactation)

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.

Information for Patients

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

1. You should inform your physician about any prescription or non-prescription medications, alcohol, or drugs you are now taking or are planning to take during your treatment with gabapentin.
2. No teratogenic effects have been found in animals. However, the risk to the human fetus 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 gabapentin (see **section 4.6**).
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 **section 4.6**).
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 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.
6. Prior to initiation of treatment with gabapentin, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity such as fever or lymphadenopathy may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

4.5 Interaction with other medicines and other forms of interaction

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

Anticonvulsants

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).

Oral Contraceptives

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

Antacid

Co-administration of gabapentin with antacid reduced gabapentin bioavailability by about 20% (N = 16). It is recommended that gabapentin be taken about 2 hours following antacid administration.

Cimetidine

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.

Probenecid

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 **section 4.4**). Morphine pharmacokinetic parameter values were not affected by administration of gabapentin 2 hours after morphine. The magnitude of interaction at other doses is not known.

4.6 Fertility, pregnancy and lactation

Pregnancy - Category B3

Gabapentin crosses the human placenta.

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an anti-epileptic medicinal product.

Data from an observational study, which included more than 1,700 pregnancies exposed to gabapentin based on routinely collected data from administrative and medical registers in Denmark, Finland, Norway, and Sweden, do not suggest substantially increased risks of major congenital malformations, adverse birth outcomes, or abnormal postnatal neurodevelopmental outcomes in gabapentin-exposed pregnancies.

For major congenital malformations, the adjusted prevalence ratios (aPRs) and 95% confidence intervals (CI) in the standard meta-analysis for first trimester gabapentin exposed vs. unexposed to antiepileptic drugs was 0.99 (0.80-1.23).

Overall, there were no statistically significant findings for stillbirth, small for gestational age, low Apgar score, and microcephaly. The aPRs were 1.21 (1.02-1.44) for low birth weight, 1.16 (1.00-1.35) for preterm birth.

In paediatric population exposed in utero, the study did not provide evidence of an increased risk for neurodevelopmental outcomes, such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), and intellectual disabilities.

Neonatal withdrawal syndrome has been reported in newborns exposed in utero to gabapentin. Co-exposure to gabapentin and opioids during pregnancy may increase the risk of neonatal withdrawal syndrome.

Gabapentin should be used during pregnancy only if the potential benefit to the mother clearly outweighs the potential risk to the fetus.

The risk of having a child with a congenital defect as a result of anti-epileptic medication is far outweighed by the dangers to the mother and fetus of uncontrolled epilepsy.

It is recommended that:

- women on anti-epileptic drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of fetal abnormalities;
- AEDs 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 prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Studies in animals have shown reproductive toxicity.

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 fetal malformations due to gabapentin administration. Gabapentin-induced delayed ossification in the skull, vertebrae, forelimbs and hind limbs, indicative of fetal growth retardation, was reported in the offspring of mice administered gabapentin during organogenesis, and rats administered gabapentin during mating and throughout gestation. An increased incidence of hydroureter and/or hydronephrosis was observed in rats, and these findings have been associated with delayed development. 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 female 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 fetus was observed.

Breast-feeding

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 hydroureter 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 medication, taking into account the importance of the drug to the mother. Gabapentin should be used in nursing mothers only if the benefits clearly outweigh the risks.

Fertility

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

4.7 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.

4.8 Undesirable effects

Epilepsy
Adults and Children Older than 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 effects associated with the use of gabapentin in combination with other anti-epileptic drugs, 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 effects most commonly associated with withdrawal were somnolence, ataxia, fatigue, nausea and/or vomiting, and dizziness.

Incidence in Controlled Clinical Trials

Table 4 lists the 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 anti- epileptic drug therapy. Adverse effects were usually mild to moderate in intensity.

Table 4: Summary of Treatment-emergent Signs and Symptoms in ≥1% of Gabapentin-treated Patients in Adjunctive Therapy Placebo-Controlled Studies

Body System/Adverse Event	Gabapentin[a] N = 543 Patients		Placebo[a] N = 378 Patients	
	Number	%	Number	%
Body as a Whole				
Back pain	10	1.8	2	0.5
Fatigue	60	11.0	19	5.0
Fever	7	1.3	5	1.3
Viral infection	7	1.3	8	2.1
Peripheral oedema	9	1.7	2	0.5
Weight increase	16	2.9	6	1.6
Cardiovascular				
Vasodilation	6	1.1	1	0.3
Digestive System				
Abdominal pain	10	1.8	9	2.4
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
Hematologic and Lymphatic				
Leukopenia	6	1.1	2	0.5
WBC decreased	6	1.1	2	0.5
Musculoskeletal System				
Fracture	6	1.1	3	0.8
Myalgia	11	2.0	7	1.9
Nervous System				
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	4	1.1
Dizziness	93	17.1	26	6.9
Dysarthria	13	2.4	2	0.5
Emotional lability	6	1.1	5	1.3
Headache	44	8.1	34	9.0
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
Respiratory System				
Coughing	10	1.8	5	1.3

Body System/Adverse Event	Gabapentin[a] N = 543 Patients		Placebo[a] N = 378 Patients	
	Number	%	Number	%
Pharyngitis	15	2.8	6	1.6
Rhinitis	22	4.1	14	3.7
Skin and Appendages				
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
Special Senses				
Amblyopia	23	4.2	4	1.1
Diplopia	32	5.9	7	1.9
Urogenital System				
Impotence	8	1.5	4	1.1

[a] Includes concomitant anti-epileptic drug therapy

Other Adverse Effects 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.
Haematologic 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, most often described as a visual disturbance.

Children from 3 to 12 Years of Age

The most commonly observed adverse effects reported with the use of gabapentin in combination with other anti-epileptic drugs 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 aged 3 to 12 years who received gabapentin in pre-approval clinical trials discontinued treatment because of an adverse event. The adverse effects 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)

Body System/Adverse Event	Gabapentin[a] N = 119 %	Placebo[a] N = 128 %
Body as a Whole		
Viral infection	10.9	3.1
Fever	10.1	3.1
Weight increase	3.4	0.8
Fatigue	3.4	1.6
Digestive System		
Nausea and/or vomiting	8.4	7.0
Nervous System		
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
Respiratory System		
Bronchitis	3.4	0.8
Respiratory infection	2.5	0.8

[a] Plus background anti-epileptic drug 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 effects 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.
Haematologic and Lymphatic Systems:	Coagulation defect.
Nervous System:	Aura disappeared, occipital neuralgia.
Psychobiologic Function:	Sleepwalking.
Respiratory System:	Pseudo-croup, hoarseness.

Neuropathic Pain

Adults Older than 18 Years of Age

The most commonly observed adverse effects reported with the use of gabapentin in adults older than 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 effects most commonly associated with withdrawal were dizziness (4.4%), somnolence (2.9%), nausea (1.3%) and ataxia (1.0%).

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 ≥1% of Gabapentin-treated Patients in Neuropathic Pain Placebo-controlled Studies

Body System/Adverse Event	Gabapentin N = 821 Patients		Placebo N = 537 Patients	
	Number	%	Number	%
Body as a Whole				
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	8	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
Digestive System				
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
Metabolic and Nutritional				
Peripheral oedema	44	5.4	14	2.6
Weight gain	14	1.7	0	0.0
Nervous System				
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
Respiratory System				
Dyspnoea	9	1.1	3	0.6
Pharyngitis	15	1.8	7	1.3

Body System/Adverse Event	Gabapentin N = 821 Patients		Placebo N = 537 Patients	
	Number	%	Number	%
Skin and Appendages				
Rash	14	1.7	4	0.7
Special Senses				
Amblyopia	15	1.8	2	0.4

Post-marketing Experience

The following adverse effects 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 effects reported include blood creatine phosphokinase increased, rhabdomyolysis, acute kidney failure, agitation, renal impairment, allergic reaction including urticaria, alopecia, anaphylaxis, anaemia, angioedema, convulsions, drug rash with eosinophilia and systemic symptoms, depersonalisation, urinary incontinence, pancreatitis, erythema multiforme, fall, hypersensitivity including systemic reactions, hyponatraemia, jaundice, loss of consciousness, movement disorders such as choreoathetosis, dyskinesia and dystonia, myoclonus, speech disorder, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia), palpitation, tachycardia, Stevens-Johnson syndrome, thrombocytopenia, tinnitus, hyperglycaemia and hypoglycaemia (most often observed in patients with diabetes), breast hypertrophy, gynaecomastia, cardiac arrest, chest pain, abnormal liver function and symptoms of psychosis such as delusions, hallucinations, and thinking abnormal.

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

After discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed in some patients. Most frequently reported symptoms include anxiety, insomnia, nausea, pains, sweating, tremor, headache, depression, feeling abnormal, dizziness, and malaise (see **section 4.4 Special warnings and precautions for use**).

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 medication.

The following adverse effects have not been identified as specific to gabapentin. However, anti-epileptic drugs have been associated with an increased risk of suicidal behaviour, suicidal ideation and emergence or worsening of existing depression.

Reporting of Suspected Adverse Reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

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 drug-related toxic effects were seen in monkeys which received gabapentin doses up to 1250 mg/kg orally.

Signs and Symptoms

Symptoms of an overdose included somnolence, ataxia, dizziness, double vision, nystagmus, slurred speech, drowsiness, loss of consciousness, 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.

Treatment of Overdosage

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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Other analgesics and antipyretics, ATC code: N02BF01

Mechanism of Action

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 medications that interact with GABA synapses including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. *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 drug or neurotransmitter receptors of the brain including $GABA_A$, $GABA_B$, 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 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.

Clinical Efficacy

Partial Seizures

Adults

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 anti-epileptic drugs at therapeutic levels and were observed on their established anti-epileptic 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, given as three divided doses 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 gabapentin, given as three divided doses (N = 101), with placebo (N = 98). Additional smaller 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 (i.e. 300 mg on Day 1, 600 mg on Day 2, 900 mg on Day 3). Seven hundred and eighty-one patients (titrated = 383, non-titrated = 388) involved in the study had partial seizures which were not adequately controlled with one or two other anti-epileptic 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 (i.e. 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 non-titrated group reporting the higher incidence, however, it did not lead to increased discontinuation in this group.

Paediatric Patients

The safety and efficacy of gabapentin administered as adjunctive therapy for the treatment of partial seizures in paediatric 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 anti-epileptic drugs. After a 6-week baseline phase, during which patients received their prescribed anti-epileptic drugs, 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 AEDs. 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.

Neuropathic Pain

Adults

The efficacy and safety of gabapentin for the treatment of neuropathic pain in adults older than 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/day, 2400 mg/day 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.

Paediatric Use

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.

5.2 Pharmacokinetic properties

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, i.e. 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 mg to 600 mg three times a day, however, the differences in bioavailability are 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 mg/day, 2400 mg/day, 3600 mg/day, 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 ± 6 L (Mean ± SD). In patients with epilepsy, steady-state pre-dose (C_{min}) concentrations of gabapentin in the cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Biotransformation and Elimination

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. 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.

Dose adjustment in patients with compromised renal function or in those undergoing haemodialysis is recommended (see **section 4.2**).

Special Populations

Patients with Renal Insufficiency

Subjects with renal insufficiency (mean creatinine clearance ranging from 13 mL/min to 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 (CLcr) >60 mL/min) to 52 hours (CLcr <30 mL/min) and gabapentin renal clearance ranged from about 90 mL/min (CLcr >60 mL/min) to about 10 mL/min (CLcr <30 mL/min). Gabapentin dosage should be adjusted in patients with compromised renal function (see **section 4.2**).

Patients on Haemodialysis

In a study in anuric patients, the elimination half-life of gabapentin on non-dialysis 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 **section 4.2**).

Elderly (≥65 years)

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 younger than 30 years of age to about 125 mL/min in those older than 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.

Children and Adolescents

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

5.3 Preclinical safety data

Genotoxicity

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.

Carcinogenicity

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 2 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 gabapentin concentrations and areas under the concentration time curve in rats at 2000 mg/kg/day were 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 were low-grade malignancies, which 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill:
Lactose monohydrate
Purified talc
Maize starch

100 mg capsule shell
Gelatin
Titanium dioxide

300 mg capsule shell
Gelatin
Titanium dioxide
Iron oxide yellow

400 mg capsule shell
Gelatin
Titanium dioxide
Iron oxide yellow
Iron oxide red

Printing ink
Shellac
Iron oxide black
Propylene glycol
Ammonium hydroxide.

6.2 Incompatibilities

None stated.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Gabapentin capsules are available in blister packs of 100.

6.6 Special precautions for disposal

None stated.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Max Health Ltd
PO Box 44452
Pt Chevalier, Auckland 1246

Telephone: (09) 815 2664.

9. DATE OF FIRST APPROVAL

13 June 2024

10. DATE OF REVISION OF THE TEXT

13 June 2024

Summary Table of Changes

Sections changed	Summary of new information
	New