NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Arrow - Gabapentin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Arrow - Gabapentin capsules contain 100 mg, 300 mg or 400 mg of gabapentin.

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
100 mg: White opaque capsule marked in blue ink with '⌬' on the body and "GA 100" on the cap.

300 mg: Yellow opaque capsule marked in blue ink with '⌬' on the body and "GA 300" on the cap.

400 mg: Orange opaque capsule marked in blue ink with '⌬' on the body and "GA 400" on the cap

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Dose

EPILEPSY

Adults and children aged 3 years and over:

Gabapentin is indicated as an add-on therapy for the treatment of partial seizures, with or without secondary generalised tonic-clonic seizures, in adults and children aged 3 years and above who have not achieved adequate control with standard anti-epileptic drugs (AEDs).

NEUROPATHIC PAIN

Gabapentin is indicated for the treatment of neuropathic pain in adults over 18 years of age.

4.2 Dose and method of administration
EPILEPSY

Initiation of treatment should be as add-on therapy.

Adults and children over 12 years of age

In controlled clinical trials, the effective dose range was 900 to 1,800 mg/day given in three divided doses.

Therapy may be initiated by administering 300 mg capsules three times a day on Day 1 or by titrating the dose. Titration to an effective dose can take place rapidly, over a few days, giving 300 mg capsules on Day 1, 300 mg capsules twice a day on Day 2, 300 mg capsules 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 AEDs 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 three times a day up to 2400 mg/day. Dosages up to 2,400 mg/day have been well tolerated in long-term open label clinical studies. The maximum time between doses in the three times daily 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 the following table.

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 aged 3 to 12 years

Weight range (kg)	Daily dose (mg/day)
17 – 25	600
26 – 36	900
37 – 50	1200
51 - 72	1800

NEUROPATHIC PAIN

Adults over 18 years of age

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

Special Populations

Elderly patients

The dosage of gabapentin should be adjusted in elderly patients with age-related reduction in renal function.

Impaired renal function

Dosage adjustment is recommended in patients with compromised renal function as described in the following table and/or those undergoing haemodialysis.

Table 2: Dosage of gabapentin in adults based on renal function

Creatinine clearance (mL/minute)	Total daily dose[a] (mg/day)
≥ 80	900 – 3,600
50 – 79	600 – 1,800
30 – 49	300 - 900
15 - 29	150[b] - 600
< 15	150[b] - 300

[a] Total daily dose should be administered as a three times daily regimen. Doses used to treat patients with normal renal function (creatinine clearance > 80 mL/minute) range from 900 to 3,600 mg/day. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 mL/minute).

[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 to 400 mg is recommended, then 200 to 300 mg of gabapentin following each 4 hours of haemodialysis.

Serum monitoring

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 AEDs

without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other AEDs.

Discontinuation
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.

Method of administration
Arrow - Gabapentin Capsules should be swallowed whole with water, with or without food.

4.3 Contraindications
Arrow - Gabapentin is contraindicated in patients with known hypersensitivity to gabapentin or any component of this preparation (see section 5.1 Pharmacodynamic properties).

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 that there is a need for dose reduction, discontinuation, or substitution of alternative anticonvulsant medication, this should be done gradually over a minimum of 1 week.

Gabapentin is not generally 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 accidential 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
Gabapentin has been associated with central nervous system (CNS) depression including sedation, somnolence, loss of consciousness as well as serious cases of respiratory depression. This may occur without concomitant opioid use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment and the elderly are at higher risk of experiencing these severe adverse effects. Concomitant use of CNS depressants with gabapentin increases the risk of respiratory depression.

Patients who require concomitant treatment with opioids may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately (see section 4.5 Interaction with other medicines and other forms of interaction).

Suicidal Behaviour and Ideation
Antiepileptic 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 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: 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 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 (DRESS)

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

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient

should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Anaphylaxis
Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue Arrow – 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 observed for possible signes of gabapentin abuse.

Use in children
The safety and effectiveness of gabapentin in children with epilepsy below the age of 3 years have not been established. Gabapentin is not recommended for treatment of neuropathic pain in children below the age of 18 years as the safety and effectiveness in this population have not been established.

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

1. Inform your physician about any prescription or non-prescription medications, alcohol, or drugs you are now taking or plan to take during your treatment with gabapentin.
2. No teratogenic effects have been found in animals. However, the risk to the human foetus cannot be dismissed. So, 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 breastfeeding an infant (see section 4.6).
4. Until you experience how this medication affects you, do not drive a car or operate potentially dangerous machinery.
5. You should not allow more than 12 hours between gabapentin doses. 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 and/or sedation associated with gabapentin and opioid use. These effects would be of particular concern in elderly patients.

Anti-epileptic drugs
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 oestradiol 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 daily, 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 Special warnings and precautions for use). 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.

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.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy (Category B1)
Gabapentin crosses the human placenta.

Congenital malformations and adverse pregnancy outcomes have been reported with gabapentin use, however there are no adequate and well-controlled studies in pregnant women and no definite conclusions can be made as to whether gabapentin is causally associated with an increased risk of congenital malformations or other adverse developmental outcomes when taken during pregnancy. The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product.

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

The risk of having a child with a congenital defect 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 drugs (AEDs) receive pre-pregnancy counselling with regard to the risk of foetal 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 4 weeks prior to and continue for 12 weeks after conception;
- specialist pre-natal diagnosis including detailed mid-trimester ultrasound should be offered.

Use in lactation
Gabapentin is excreted in human milk.

In a peri- and post-natal study in rats at doses of 500, 1,000 and 2,000 mg/kg/day, there was a dose related increase in the incidence of hydroureter in 21-day old pups.

Because of the unknown effect of gabapentin and the potential for its serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, 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/kd/day.

Reproduction studies in mice at doses up to 3,000 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. Gabapentin-induced delayed ossification in the skull, vertebrae, forelimbs and hind limbs, indicative of foetal 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 2,400 mg/day.

In female rabbits given 60, 300 or 1,500 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.

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 over 12 years of age
Gabapentin has been evaluated for safety in approximately 2,000 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 AEDs, not seen in an equivalent frequency among placebo-treated patients, were somnolence, dizziness, ataxia, fatigue and nystagmus.

Approximately 7% of the 2,074 individuals who received gabapentin in the pre-marketing 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
The following table 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 AED therapy. Adverse events were usually mild to moderate in intensity.

Table 3 Adverse events reported in at least 1% of participants in gabapentin placebo-controlled trials

Body System and adverse event	Gabapentin[a] N = 543		Placebo[a] N = 378	
	No of patients	%	No of patients	%
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
Haematologic and lymphatic				
Leukopenia	6	1.1	2	0.5
WBC decreased	6	1.1	2	0.5
Metabolic and nutritional				
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
Co-ordination 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
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
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 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 summarized below.

Body as a whole:	asthenia, malaise, facial oedema
Cardiovascular system:	hypertension
Digestive system:	flatulence, anorexia, gingivitis
Haemic 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 events reported with the use of gabapentin in combination with other AEDs 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 events most commonly associated with withdrawal in children were somnolence (1.4%), hyperkinesia (1.0%) and hostility (1.0%).

Table 4 Treatment-emergent adverse event incidence in children aged 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 and 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] Including concomitant anti-epileptic drug therapy

Other adverse events observed during clinical studies

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, abnormal thinking, vertigo, rash and amblyopia.

Of the 821 adults who received gabapentin in the painful diabetic peripheral neuropathy and post-herpetic neuralgia trial, 13.2% discontinued treatment because of an adverse event. The adverse events most commonly associated with withdrawal were dizziness (4.4%), somnolence (2.9%), ataxia (1.0%) 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 5 Summary of treatment-emergent signs and symptoms in 1% of gabapentin treated patients in neuropathic pain placebo-controlled studies

COSTART Body System and adverse event	Gabapentin N = 821		Placebo N = 537	
	No of patients	%	No of patients	%
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
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 events have been reported in patients receiving gabapentin post-marketing. However, the data is 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 blood creatine phosphokinase increased, rhabdomyolysis, acute kidney failure, agitation, renal impairment, allergic reaction including urticaria, alopecia, anaemia, angioedema, drug rash with eosinophilia and systemic symptoms, fall, hypersensitivity including systemic reactions, hyponatraemia, jaundice, loss of consciousness, blood glucose fluctuations in patients with diabetes, cardiac arrest, chest pain, convulsions, depersonalisation, erythema multiforme, movement disorders such as choreoathetosis, dyskinesia and dystonia, myoclonus, palpitation, pancreatitis, renal impairment, speech disorder, sexual dysfunction(including changes in libido, ejaculation disorders and anorgasmia), Stevens-Johnson syndrome, tachycardia, 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 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 drug.

The following adverse effects have not been identified as specific to gabapentin. However, antiepileptic 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://nzphvc.otago.ac.nz/reporting/).

4.9 Overdose
An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, and

hypoactivity or excitation. No deaths or drug-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.

Treatment
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.

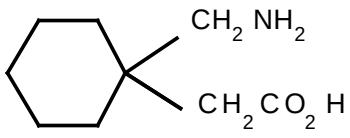
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiepileptics, other antiepileptics, ATC code: N03AX12

Gabapentin is a white to off-white crystalline solid, freely soluble in water and in both basic and acidic aqueous solutions. The chemical name of gabapentin is 1-(aminomethyl) cyclohexaneacetic acid. Its structural formula is:



$C_9H_{17}NO_2$ Molecular weight: 171.24 CAS: 60142-96-3

The mechanism by which gabapentin exerts its anticonvulsant action is unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but its mechanism of action is different from that of several other drugs 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 (NMDA) 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 and Safety

Epilepsy

The effectiveness of gabapentin as adjunctive therapy was established in three multicentre, 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 of more anti-epileptic drugs (AEDs) at therapeutic levels and were observed on their established AED 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 1,200 mg/day (in 3 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 1,200 mg/day (in 3 divided doses) gabapentin (N = 101) with placebo (N = 98). Additional smaller gabapentin dosage groups (600 mg/day, N = 53; 1,800 mg/day, N = 54) were also studied for information regarding dose response. Responder rate was higher in the gabapentin 1,200 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 1,800 mg group (26%) was statistically significantly superior to the placebo rate. Response ratio was better in the gabapentin 1,200 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 1,800 mg/day group (-0.222) than in the 1,200 mg/day group, with the 1,800 mg/day group achieving statistical significance compared to the placebo group.

A third study compared gabapentin 900 mg/day (in 3 divided doses) (N = 111) and placebo (N = 109). An additional gabapentin 1,200 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 1,200 mg/day gabapentin (-0.184) compared to placebo.

A 1-week, prospective, multicentre, 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 3 days (i.e. 300 mg on Day 1, 600 mg on Day 2, 900 mg on Day 3). 781 patients (titrated = 383, non-titrated = 388) involved in the study had partial seizures, which were not adequately controlled with one or two other AEDs. For the modified intention-to-treat (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.

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 AEDs. After a 6-week baseline phase, during which patients received their prescribed AEDs, 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 response ratio in 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 response ratio 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 response ratio 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

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 1,800 mg, 2,400 mg and 3,600 mg/day (in three divided doses) consecutively over the first 4 weeks of the study. Patients were then maintained at the maximum dose that was tolerated for the remaining 4 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.

5.2 Pharmacokinetic properties

Pharmacokinetics

All pharmacological actions following gabapentin administration are due to the activity of the parent compound.

Absorption

Gabapentin bioavailability is not dose proportional, i.e., as dose is increased, bioavailability is decreased. 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 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, 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 ± 6 L (mean ± SD). In patients with epilepsy, steady-state pre-dose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Biotransformation and Elimination

Gabapentin is not appreciably metabolised in humans.

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. 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 section 4.2 Dose and method of Administration).

Special populations

Patients with renal insufficiency

Subjects with renal insufficiency [mean creatinine clearance (Cl_{cr}) ranging from 13 - 114 mL/minute (min)] were administered a 400 mg oral dose of gabapentin. The mean gabapentin half-life ranged from about 6.5 hours (Cl_{cr} > 60 mL/min) to 52 hours (Cl_{cr} < 30 mL/min) and gabapentin renal clearance ranged from about 90 mL/min (Cl_{cr} > 60 mL/min) to about 10 mL/min (Cl_{cr} <30mL/min). Gabapentin dosage should be adjusted in patients with compromised renal function (see section 4.2 Dose and method of Administration).

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 Dose and method of 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 aged-related compromised renal function.

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

5.3 Preclinical safety data
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.

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 drug 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.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose, maize starch, purified talc, gelatin, titanium dioxide, iron oxide yellow (300 mg and 400 mg capsules only), iron oxide red (400 mg capsules only) and Opacode A-R-10561FD blue printing ink.

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Blister pack: 24 months

Bottle: 36 months

6.4 Special precautions for storage
Store below 25^{o}C.

6.5 Nature and contents of container
PVC/PVdC/Aluminium foil blister strips. Pack size of 100 capsules.

HDPE bottles. Pack sizes of 100 and 500 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited
PO Box 128 244
Remuera
Auckland 1541
Telephone: 0800 800 097

9. DATE OF FIRST APPROVAL

2 November 2006

10. DATE OF REVISION OF THE TEXT

19 February 2018

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
	Update to the SPC-style format
4.4	Updated to include the risk of respiratory depression with gabapentin alone, in the absence of concomitant opioid use.
4.5, 4.6, 4.8, 5.3	Updated