SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

NEURONTIN® 100 capsules

NEURONTIN® 300 capsules

NEURONTIN® 400 capsules

NEURONTIN® 600 tablets

NEURONTIN® 800 tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

NEURONTIN 100: Each capsule contains 100 mg gabapentin.

NEURONTIN 300: Each capsule contains 300 mg gabapentin.

NEURONTIN 400: Each capsule contains 400 mg gabapentin.

NEURONTIN 600: Each tablet contains 600 mg gabapentin.

NEURONTIN 800: Each tablet contains 800 mg gabapentin.

NEURONTIN capsules contain sugar (lactose monohydrate).

NEURONTIN tablets are sugar free.

Excipients with known effect

Each NEURONTIN 100 capsule contains 14,25 mg lactose monohydrate.

Each NEURONTIN 300 capsule contains 42,75 mg lactose monohydrate.

Each NEURONTIN 400 capsule contains 57,00 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsules

NEURONTIN 100: White, opaque, hard gelatine capsules imprinted in blue ink with “Neurontin 100 mg” on the cap and “VLE” on the body.

NEURONTIN 300: Light yellow, opaque, hard gelatine capsules imprinted in grey ink with “Neurontin 300 mg” on the cap and “VLE” on the body.

NEURONTIN 400: Grey-orange, opaque, hard gelatine capsules imprinted in grey ink with “Neurontin 400 mg” on the cap and “VLE” on the body.

Film-coated tablets

NEURONTIN 600: White, elliptical film-coated tablet with bisecting score on both sides, debossed with “NT” and “16” on one side.

NEURONTIN 800: White, elliptical film-coated tablet with bisecting score on both sides, debossed with “NT” and “26” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

NEURONTIN is indicated in controlling both simple and complex partial seizures with or without secondary generalised tonic-clonic seizures in adults and children over 12 years of age.

NEURONTIN is indicated as adjunctive therapy with standard anti-epileptic medicines in patients who have not achieved adequate seizure control with these medicines used alone or in combination.

4.2 Posology and method of administration

General

When in the judgment of the medical practitioner there is a need for dose reduction, discontinuation, or substitution of alternative anticonvulsant medicine, this should be done gradually over a minimum of one week.

It is unnecessary to monitor NEURONTIN plasma concentrations to optimise NEURONTIN therapy.

NEURONTIN may be used in combination with phenobarbital, phenytoin, valproic acid and carbamazepine without concern for alteration of the plasma concentrations or serum concentrations of NEURONTIN or the other anti-epileptic medicines.

Posology

Epilepsy

Adults and children over 12 years of age

Usual effective dose: 900 – 1 800 mg/day in three divided doses with not more than 12 hours between doses.

Since titration to an effective dose can progress rapidly, this may be accomplished in as few as three

days using one of the following approaches:

In clinical trials, the effective dosing range was 900 mg to 1 000 mg/day.

Therapy should be initiated by titrating the dose as described in Table 1. Thereafter, the dose can be increased in three equally divided doses up to a maximum dose of 1 800 mg/day.

Table 1

Dosing chart – Initial titration

Dose	Day 1	Day 2	Day 3
900 mg	300 mg once a day	300 mg two times a day	300 mg three times a day

Special populations

Elderly

Elderly patients should be carefully monitored for adverse events. Elderly patients may require dosage adjustment because of declining renal function with age. Adjust according to creatinine clearance as described in Table 2.

Compromised renal function

The elimination of NEURONTIN is decreased in patients with impaired renal function.

This patient population has not been fully examined but the following guidelines are based on information derived from single doses in non-epileptic patients.

For patients with compromised renal function or those undergoing haemodialysis the following maintenance dosage is recommended.

Table 2

Renal function Creatinine clearance (mL/min)	Total daily dose (mg/day)	Dose regiment (mg)
> 60	1 200	400 three times a day
> 30 – 60	600	300 twice a day
15 – 30	300	300 once a day
< 15	150	300 every other day
Haemodialysis[a]	-	200 – 300[b]

[a] Loading dose of 300 to 400 mg

[b] Maintenance dose of 200 to 300 mg NEURONTIN following each 4 hours of haemodialysis

Paediatric population

Epilepsy

Safety and effectiveness in children under 12 years of age have not been established.

Method of administration

For oral use.

NEURONTIN may be given ~~orally~~ with or without food.

4.3 Contraindications

- Hypersensitivity to gabapentin or to any of the excipients of NEURONTIN (listed in section 6.1).
- Safety and efficacy have not been established in children 12 years of age or younger.
- Pregnancy and lactation (see section 4.6).
- Severe impaired renal function.

4.4 Special warnings and precautions for use

General

Although there is no convincing evidence of rebound seizures with NEURONTIN, abrupt withdrawal of NEURONTIN in epileptic patients may precipitate *status epilepticus*.

NEURONTIN is not generally considered effective in the treatment of absence seizures.

Do not allow more than 12 hours between NEURONTIN doses to prevent breakthrough convulsions.

NEURONTIN 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 NEURONTIN.

Concomitant use with opioids and other CNS depressants

Patients who require concomitant treatment with central nervous system (CNS) depressants, including opioids, should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression. Patients who use NEURONTIN and morphine concomitantly may experience increases in NEURONTIN concentrations. The dose of NEURONTIN, or concomitant treatment with CNS depressants including opioids, should be reduced appropriately (see section 4.5).

Caution is advised when prescribing NEURONTIN 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 NEURONTIN 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]).

Respiratory depression

NEURONTIN has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.

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-epileptic medicines including NEURONTIN.

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. NEURONTIN should be discontinued if an alternative aetiology for the signs or symptoms cannot be established.

Anaphylaxis

NEURONTIN 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 NEURONTIN and seek immediate medical care should they experience signs or symptoms of anaphylaxis (see section 4.8).

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with NEURONTIN in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicines has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known, and the available data do not exclude the possibility of an increased risk for NEURONTIN.

Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients and caregivers should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Misuse, abuse potential or dependence

Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of NEURONTIN misuse, abuse or dependence (development of tolerance, dose escalation, intentional overdose, drug-seeking behaviour have been reported).

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 NEURONTIN when co-administered with CNS depressants, including opioids. In some of these reports, the authors considered the combination of NEURONTIN 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 with substance abuse disorders (see section 4.4).

Morphine

In a study involving healthy volunteers (n=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg NEURONTIN capsule, the mean NEURONTIN AUC increased by 44 % compared to NEURONTIN administered without morphine. The clinical significance of such changes has not been defined. Morphine pharmacokinetic parameter values were not affected by administration of NEURONTIN 2 hours after morphine. The observed opioid-mediated side effects associated with morphine plus NEURONTIN in the volunteers did not differ significantly from morphine plus placebo. The magnitude of interaction at other doses is not known (see section 4.4).

There is no interaction between NEURONTIN and phenobarbital, phenytoin, valproic acid or carbamazepine. NEURONTIN steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving anti-epileptic medicines.

Co-administration of NEURONTIN with oral contraceptives containing norethindrone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either component.

Co-administration of NEURONTIN with a magnesium-and aluminium-containing antacid reduces NEURONTIN bioavailability by approximately 20 %. It is recommended that NEURONTIN be taken about two hours before or after antacid administration.

Renal excretion of NEURONTIN is unaltered by probenecid.

A slight decrease in renal excretion of NEURONTIN observed when it is co-administered with cimetidine is not expected to be of clinical importance.

Laboratory tests

False positive tests for proteinuria may occur with the Ames Multistix-SG dipstick test when NEURONTIN is added to other anticonvulsant medicines. To determine urinary protein, the more specific sulfosalicylic acid precipitation procedure is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

NEURONTIN crosses the human placenta. There are, however, no adequate and well-controlled studies in pregnant women.

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. NEURONTIN did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times, respectively, the daily human dose of 3 600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m^2 basis). Because animal reproduction studies are not always predictive of human response, NEURONTIN should not be used during pregnancy.

Breastfeeding

NEURONTIN is excreted in human milk. Because the effect on the nursing infant is unknown, NEURONTIN should not be used in breastfeeding mothers.

Fertility

There is no effect on fertility in animal studies.

4.7 Effects on ability to drive and use machines

NEURONTIN frequently causes dizziness and somnolence. Therefore, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicine affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

Epilepsy

The following side effects have been reported:

The most frequent clinical adverse events occurring in all clinical studies were somnolence, dizziness, ataxia, headache, nystagmus, tremor, fatigue, diplopia, nausea and/or vomiting and rhinitis.

Tabulated summary of adverse reactions

From data drawn from placebo-controlled studies, adverse events are listed in descending order of frequency both by bodily system and by associated adverse events:

Very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1 000 to < 1/100; rare ≥ 1/10 000 to < 1/1 000; very rare < 1/10 000.

MedDRA System Organ Class	Frequency	Undesirable effect
Infections and infestations	Common	Viral infection, respiratory infection
Blood and lymphatic system disorders	Common	Leukopenia
Metabolism and nutrition disorders	Common	Increased appetite
Psychiatric disorders	Common	Confusion, depression, emotional lability, nervousness, abnormal thinking
Nervous system disorders	Very common	Ataxia, dizziness, somnolence
	Common	Amnesia, abnormal coordination, dysarthria, insomnia, headache, nystagmus, tremor
Eye disorders	Common	Amblyopia, diplopia
Vascular disorders	Common	Vasodilation
Respiratory, thoracic and mediastinal disorders	Common	Dyspnoea, cough, pharyngitis, rhinitis
	Rare	Respiratory depression

Gastrointestinal disorders	Common	Abdominal pain, constipation, dental abnormalities, diarrhoea, dyspepsia, dry mouth or throat, nausea, vomiting
Skin and subcutaneous tissue disorders	Common	Acne, pruritus, rash
Musculoskeletal and connective tissue disorders	Common	Back pain, myalgia, twitching
Reproductive system and breast disorders	Common	Impotence
General disorders and administration site conditions	Very common	Fatigue
	Common	Fever, peripheral oedema
Investigations	Common	Decreased WBC (white blood cell count), weight increase
Injury, poisoning and procedural complications	Common	Abrasion, fracture

Post-marketing experience

The following cases have been reported:

MedDRA System Organ Class	**Undesirable effect**
Blood and lymphatic system disorders	Thrombocytopenia
Immune system disorders	Allergic reaction including urticaria, anaphylaxis, anaphylactoid reaction, hypersensitivity including systemic reactions
Metabolism and nutrition disorders	Hyperglycaemia and hypoglycaemia (most often observed in patients with diabetes), hyponatraemia
Psychiatric disorders	Hallucinations, agitation
Nervous system disorders	Movement disorders such as choreoathetosis, dyskinesia, and dystonia, spastic torticollis and myoclonus, loss of consciousness
Ear and labyrinth disorders	Tinnitus

Cardiac disorders	Palpitation, chest pain
Gastrointestinal disorders	Pancreatitis
Hepatobiliary disorders	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	Alopecia, angioedema, erythema multiforme, Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Rhabdomyolysis
Renal and urinary disorders	Acute kidney failure, urinary incontinence
Reproductive system and breast disorders	Breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)
General disorders and administration site conditions	Adverse events following the abrupt discontinuation of NEURONTIN have also been reported. The most frequently reported events were anxiety, insomnia, nausea, sweating, depression, headache, pain, tremor, agitation, panic attacks, diarrhoea, dizziness, tachycardia, confusion and generalised oedema. Sudden unexplained deaths have been reported where a causal relationship to treatment with NEURONTIN has not been established.
Investigations	Elevated liver function tests (LFTs), increased blood creatine phosphokinase
Injury, poisoning and procedural complications	Fall

Some of these could represent seizure-related deaths in which the seizure was not observed e.g. at night. This represents an incidence of 0,0038 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained deaths in patients with epilepsy not receiving NEURONTIN (ranging from 0,0005 for the general population of epileptics, to 0,003 for a clinical trial population similar to that

in the NEURONTIN program, to 0,005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or raise further concern depends on comparability of the populations reported upon to the NEURONTIN cohort and the accuracy of the estimates provided.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

No specific information is available on the treatment of overdose with NEURONTIN, although haemodialysis has been shown to be effective in eliminating NEURONTIN. Treatment is symptomatic and supportive, consistent with established medical care.

Overdoses of NEURONTIN up to 49 g ingested at one time have been reported in four people, all of whom recovered fully.

Symptoms of overdose included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy and mild diarrhoea.

An oral lethal dose of NEURONTIN was not identified in mice and rats given doses as high as 8 000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity or excitation.

Reduced absorption of NEURONTIN at higher doses may limit medicine absorption and hence minimise toxicity at the time of overdosing.

In patients with renal impairment haemodialysis may be indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.5 Anticonvulsants, including anti-epileptics

Mechanism of action

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either $GABA_A$ or $GABA_B$ receptors nor does it alter

the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with high affinity to the α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other medicine targets other than α2δ.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to α2δ through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

5.2 Pharmacokinetic properties

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Absolute bioavailability of 300 mg and 400 mg gabapentin capsules is approximately 55 %. Food has no effect on gabapentin pharmacokinetics. Gabapentin elimination parameters are independent of dose.

However, the extent of gabapentin absorption decreases with increasing dose. Following doses of 300 mg and 600 mg gabapentin, absolute bioavailability is 57 % and 42 %, respectively. Gabapentin bioavailability is not dose proportional. In normal volunteers the elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours. Although plasma gabapentin concentrations were generally between 2 μg/mL and 20 μg/mL in clinical studies, such concentrations were not predictive of safety or efficacy.

Gabapentin is not bound to plasma proteins and has an apparent volume of distribution of 57,7 L. In patients with epilepsy, gabapentin concentrations in CSF ranged from 7 – 35 % of corresponding steady-state trough plasma concentrations. Gabapentin is eliminated solely by renal excretion.

Gabapentin does not induce hepatic mixed-function oxidase enzymes responsible for medicine metabolism.

Special populations

In elderly patients, age-related alterations in renal function decrease gabapentin plasma clearance and increase gabapentin elimination half-life. Gabapentin elimination-rate constant, plasma clearance, and

renal clearance are directly proportional to creatinine clearance. Gabapentin is removed from plasma by haemodialysis.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsules

Capsule content

Lactose monohydrate

Maize starch

Talc

Capsule shell

Gelatine

Red iron oxide (400 mg)

Sodium lauryl sulphate

Titanium dioxide

Water

Yellow iron oxide (300 mg, 400 mg)

Printing ink

Indigocarmine Al salt

Shellac

Titanium dioxide

Tablets

Tablet core

Copolyvidone K

Magnesium stearate

Maize starch

Poloxamer 407

Film-coating

Hydroxypropylcellulose

Talc

Polishing agent

Candelilla wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

NEURONTIN 100, 300, 400 capsules: 36 months

NEURONTIN 600, 800 tablets: 24 months

6.4 Special precautions for storage

Store in a cool, dry place (at or below 25 °C).

6.5 Nature and contents of container

NEURONTIN 100, 300, 400 capsules: Blister packs of 100 capsules.

NEURONTIN 600, 800 tablets: Blister packs of 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

Gauteng, 1609

Manufacturer: Viatris Pharmaceuticals LLC, Vega Baja, Puerto Rico

8 REGISTRATION NUMBERS

NEURONTIN 100 capsules: 27/2.5/0598

NEURONTIN 300 capsules: 27/2.5/0599

NEURONTIN 400 capsules: 27/2.5/0600

NEURONTIN 600 tablets: 35/2.5/0099

NEURONTIN 800 tablets: 35/2.5/0100

9 DATE OF FIRST AUTHORISATION

NEURONTIN 100, 300 and 400 capsules: 24 February 1994

NEURONTIN 600 and 800 tablets: 25 April 2003

10 DATE OF REVISION OF THE TEXT

30 September 2023

BOTSWANA: S2

NEURONTIN 100 – Reg. No.: BOT1101822

NEURONTIN 300 – Reg. No.: BOT1101823

NEURONTIN 400 – Reg. No.: BOT1101824

NAMIBIA: NS3

NEURONTIN 100 – Reg. No.: 04/2.5/1234

NEURONTIN 300 – Reg. No.: 04/2.5/1235

NEURONTIN 400 – Reg. No.: 04/2.5/1236