

SCHEDULING STATUS: S3

PROPRIETARY NAME (AND DOSAGE FORM):

NEURONTIN® 100 (capsules)

NEURONTIN® 300 (capsules)

NEURONTIN® 400 (capsules)

NEURONTIN® 600 (tablets)

NEURONTIN® 800 (tablets)

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:

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.

NEURONTIN tablets are sugar free.

Excipients:

Each capsule contains lactose monohydrate, maize starch and talc. The capsule shells consist of gelatine, water, sodium laurylsulphate and the colourants titanium dioxide, yellow iron oxide (300 mg and 400 mg only) and red iron oxide (400 mg only). The printing ink consists of shellac and the colourants titanium dioxide and indigocarmine Al salt.

Each tablet contains poloxamer 407, copolyvidone K, maize starch and magnesium stearate. The film-coating consists of talc, hydroxypropylcellulose and purified water. The polishing agent is candelilla wax.

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Anticonvulsants, including anti-epileptics.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid). *In vitro* animal studies with radiolabelled gabapentin have characterized a peptide binding site in brain tissues including neocortex and hippocampus that may relate to anticonvulsant activity of gabapentin and its structural derivatives. However, the mechanism of action remains unclear.

Gabapentin at relevant clinical concentrations does not bind to other common medicines 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*. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*. Gabapentin administration to rats increases GABA turnover in several brain regions. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

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 and 600 mg gabapentin, absolute bioavailability is 57 % and 42 %, respectively. 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 litres. 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 drug metabolism.

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 DOSAGE AND DIRECTIONS FOR USE).

INDICATIONS:

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

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

CONTRAINDICATIONS:

NEURONTIN is contraindicated in patients who are hypersensitive to gabapentin or the product's excipients.

Safety and efficacy have not been established in children 12 years or less, and during pregnancy and lactation (see PREGNANCY AND LACTATION).

Severe impaired renal function.

WARNINGS:

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.

Patients who require concomitant treatment with morphine may experience increases in NEURONTIN concentrations. Patients should be carefully observed for signs of CNS depression, such as

somnolence, and the dose of NEURONTIN should be reduced appropriately (see INTERACTIONS).

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 drugs 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 etiology for the signs or symptoms cannot be established.

INTERACTIONS:

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

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.

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 WARNINGS).

Laboratory tests:

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

PREGNANCY AND LACTATION:

Usage in pregnancy:

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 of a mg/m² basis). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, NEURONTIN should not be used during pregnancy.

Usage in breastfeeding mothers:

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

DOSAGE AND DIRECTIONS FOR USE:

General:

NEURONTIN may be given orally with or without food.

When in the judgment 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.

1. Epilepsy:

Adults and children over 12 years:

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 OD ^a	300 mg BD ^b	300 mg TDS ^c

^a OD = once a day

^b BD = two times a day

^c TDS = three times a day

2. Paediatric use:

Epilepsy: Safety and effectiveness in children under 12 years has not been established.

3. Elderly:

No significant changes in the adverse event profile were found in the elderly (i.e. over 65 years of age), an increased incidence of certain adverse events cannot be excluded. However, only small numbers of patients have been studied. 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 in table under 4.

4. 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.

Renal function creatinine clearance (ml/min)	Total daily dose (mg/day)	Dose regimen (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

^aLoading dose of 300 to 400 mg

^bMaintenance dose of 200 to 300 mg gabapentin following each 4 hours of haemodialysis

5. It is unnecessary to monitor NEURONTIN plasma concentrations to optimise NEURONTIN therapy.
6. 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 agents.

SIDE EFFECTS AND SPECIAL PRECAUTIONS:

Side effects:

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.

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 $\geq 1/10$ ($\geq 10\%$), Common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$), Uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0,1\%$ and $< 1\%$), Rare $\geq 1/10000$ and $< 1/1000$ ($\geq 0,01\%$ and $< 0,1\%$), Very rare $< 1/10000$ ($< 0,01\%$).

MedDRA System Organ Class	Frequency	Undesirable effect
<i>Blood and lymphatic system disorders</i>	Common	Leukopenia
<i>Eye disorders</i>	Common	Amblyopia, diplopia
<i>Gastrointestinal disorders</i>	Common	Abdominal pain, constipation, dental abnormalities, diarrhoea, dyspepsia, mouth or

		throat dry, nausea and/or vomiting
<i>General disorders and administration site conditions</i>	Very common	Fatigue
	Common	Fever, peripheral oedema
<i>Infections and infestations</i>	Common	Viral infection, respiratory infection
<i>Injury, poisoning and procedural complications</i>	Common	Abrasion, fracture
<i>Investigations</i>	Common	WBC (white blood cell count) decreased, weight increase
<i>Metabolism and nutrition disorders</i>	Common	Increased appetite
<i>Musculoskeletal and connective tissue disorders</i>	Common	Back pain, myalgia, twitching
<i>Nervous system disorders</i>	Very common	Ataxia, dizziness, somnolence
	Common	Amnesia, coordination abnormal, dysarthria, insomnia, headache, nystagmus, tremor
<i>Psychiatric disorders</i>	Common	Confusion, depression, emotional lability, nervousness, thinking abnormal
<i>Vascular disorders</i>	Common	Vasodilation
<i>Reproductive system and breast disorders</i>	Common	Impotence
<i>Respiratory, thoracic and mediastinal disorders</i>	Common	Coughing, pharyngitis, rhinitis
<i>Skin and subcutaneous tissue disorders</i>	Common	Acne, pruritus, rash

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.

Post-marketing experience:

The following cases have been reported:

Blood and lymphatic system disorders: Thrombocytopenia.

Cardiac disorders: Palpitation, chest pain.

Ear and labyrinth disorders: Tinnitus.

Gastrointestinal disorders: Pancreatitis.

Hepatobiliary disorders: Hepatitis, jaundice.

General disorders and administrative site conditions: Adverse events following the abrupt discontinuation of gabapentin have also been reported. The most frequently reported events were anxiety, insomnia, nausea, and sweating, sudden unexplained deaths, depression, headache, pain, tremor, agitation, panic attacks, diarrhoea, dizziness, tachycardia, confusion and generalized oedema

Immune system disorders: Allergic reaction including urticaria, anaphylactic, anaphylactoid reaction and hypersensitivity including systemic reactions with eosinophilia and systemic DRESS symptoms.

Investigations: Blood glucose fluctuations in patients with diabetes, elevated liver function tests (LFTs), increased blood creatine phosphokinase.

Musculoskeletal and connective tissue disorders: Rhabdomyolysis.

Nervous system disorders: Movement disorders such as choreoathetosis, dyskinesia, and dystonia, spastic torticollis and myoclonus.

Psychiatric disorders: Hallucinations.

Skin and subcutaneous tissue disorders: Alopecia, angioedema, erythema multiforme, Stevens-Johnson syndrome.

Renal and urinary disorders: Acute kidney failure, urinary incontinence.

Reproductive system and breast disorders: Breast hypertrophy, gynaecomastia.

Special precautions:

Lactose intolerance:

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

Effects on ability to drive and use machines:

Special care should be taken by patients driving, operating machinery or performing any hazardous tasks.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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, lethargy and mild diarrhoea.

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

In patients with renal impairment haemodialysis may be indicated.

IDENTIFICATION:

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

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

NEURONTIN 400: Orange, opaque, hard gelatine capsules imprinted in grey ink with “NEURONTIN 400 mg” on the cap and “PD” on the body.

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.

PRESENTATION:

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

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

STORAGE INSTRUCTIONS:

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

KEEP OUT OF REACH OF CHILDREN.

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

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton

2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

09 May 2013

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