PROFESSIONAL INFORMATION FOR PRASEN 100, 300 & 400

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

PRASEN 100 (Capsules)

PRASEN 300 (Capsules)

PRASEN 400 (Capsules)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

PRASEN 100

Each capsule contains 100 mg gabapentin.

Contains sugar: 10,80 mg mannitol.

PRASEN 300

Each capsule contains 300 mg gabapentin.

Contains sugar: 32,40 mg mannitol.

PRASEN 400

Each capsule contains 400 mg gabapentin.

Contains sugar: 43,20 mg mannitol.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsules.

PRASEN 100

Opaque white cap and opaque white body imprinted with 'S617/100 mg' on cap with edible blue ink and "S" on body with edible green ink. Filled with a white to off white powder.

PRASEN 300

Opaque yellow cap and opaque yellow body imprinted with 'S618/300 mg' on cap with edible

blue ink and “” on body with edible green ink. Filled with a white to off white powder.

PRASEN 400

Opaque orange cap and opaque orange body imprinted with 'S619/400 mg' on cap with edible blue ink and “” on body with edible green ink. Filled with a white to off white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PRASEN 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. It is also used as adjunctive therapy in patients who have not achieved adequate seizure control with antiepileptic medicines, when used alone or in combination.

4.2 Posology and method of administration

Posology

For all indications, a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and children over the age of 12 years.

TABLE 1		
DOSING CHART – INITIAL TITRATION		
Day 1	Day 2	Day 3
300 mg once a day	300 mg twice a day	300 mg three times a day

Epilepsy

Adults and children over 12 years:

Usual effective dose: 900 – 1800 mg/day in three divides doses with not more than 12 hours between doses. Therapy should be initiated by titrating the dose as described in Table 1 above. Thereafter, the dose maybe increased to a maximum dose of 1 800 mg/day in three equally divided doses.

Elderly (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2). Elderly patients should be closely monitored for adverse events.

Special populations

Renal impairment

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

TABLE 2		
DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION		
Creatinine clearance (ml/min)	Dose (mg/day)	Dosing Regimen
> 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 gabapentin following each 4 hours of haemodialysis

Discontinuation or dose reduction of gabapentin

In accordance with current clinical practice, if gabapentin requires a dose reduction, discontinuation or substitution of alternative anticonvulsant medication, it is recommended that this should be done gradually over a minimum of one week.

Paediatric population

The safety and efficacy of **PRASEN** in children under the age of 12 years has not been

established.

Method of administration

PRASEN may be given orally with or without food and should be swallowed whole with sufficient fluid intake (e.g. a glass of water).

4.3 Contraindications

- **PRASEN** is contraindicated in patients with hypersensitivity to gabapentin or to any of the excipients (see section 6.1).
- The safety and efficacy in children under the age of 12 years has not been established.
- The safety and efficacy in pregnancy or breastfeeding has not been established (see section 4.6).
- Severe renal impairment.

4.4 Special warnings and precautions for use

Drug rash with Eosinophilia and Systemic symptoms

Drug rash with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking antiepileptic medicines including gabapentin (see section 4.8). Some of these reactions are severe and life-threatening.

DRESS typically presents with manifestations of hypersensitivity, such as fever or lymphadenopathy, even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. **PRASEN** 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 PRASEN and seek immediate medical care should they experience signs or symptoms of anaphylaxis (see section 4.8).

Suicidal ideation and behaviour

Antiepileptic medicines, including gabapentin, increase the risk of suicidal thoughts or behaviour in patients taking these medications.

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

Acute pancreatitis

Discontinuation of PRASEN should be considered if a patient develops acute pancreatitis while on treatment with PRASEN, (see section 4.8).

Seizures

Although there is no evidence of rebound seizures with gabapentin, antiepileptic medicines should not be abruptly discontinued because of the possibility of increasing seizure frequency.

Somnolence/Sedation and Dizziness

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Concomitant use with opioids

Patients who require concomitant treatment with opioids such as morphine, should be carefully observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression. The dose of PRASEN or opioids should be reduced

appropriately (see section 4.5).

Respiratory depression

Gabapentin has been associated with severe respiratory depression. Patients who have a higher risk of experiencing severe respiratory depression are those that have compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly. Dose adjustments might be necessary in these patients.

Elderly (over 65 years of age)

Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and dose should be adjusted based on creatinine clearance values in these patients.

Paediatric population

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

Abuse and dependence

Cases of abuse and dependence have been reported. Careful evaluation of patients with a history of drug abuse should be observed for possible signs of gabapentin abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance.

Laboratory tests

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic medicines, the more specific sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

4.5 Interaction with other medicines and other forms of interaction

Gabapentin is not appreciably metabolised, nor does it interfere with the metabolism of commonly co-administered antiepileptic medicines such as phenytoin, carbamazepine, valproic acid and phenobarbitone.

Morphine

When **PRASEN** is administered with morphine, patients should be observed for signs of central nervous system (CNS) depression, such as somnolence, sedation and respiratory depression.

Oral contraceptives

Concurrent use of **PRASEN** with oral contraceptives containing norethindrone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either component.

Antacids

Antacids containing magnesium and aluminium hydroxides reduced the mean bioavailability of gabapentin by about 20 %. It is recommended that **PRASEN** be taken about two hours before or after antacid administration.

Probenecid

Renal excretion of gabapentin is unaltered by probenecid.

Cimetidine

A slight decrease in renal excretion of **PRASEN** by cimetidine is observed and is not expected to be of clinical importance.

Laboratory tests

Because false positive readings were reported with the Ames N-Multistix SG® dipstick test for urinary protein when gabapentin was added to other antiepileptic medicines, the more specific

sulfosalicylic acid precipitation procedure is recommended to determine the presence of urine protein.

4.6 Fertility, pregnancy and lactation

Pregnancy

PRASEN should not be used during pregnancy as safety and efficacy has not been established.

Animal studies have shown reproductive toxicity. The potential risk in humans is not known.

Breastfeeding

PRASEN is excreted in human milk. The effect on the breastfed infant and on milk production is not known, therefore **PRASEN** 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

Gabapentin causes somnolence, drowsiness and dizziness. Patients taking **PRASEN** should not drive or operate complex machinery until they have gained sufficient experience to assess whether **PRASEN** impairs their ability to drive or operate such machinery.

4.8 Undesirable effects

a. Summary of the safety profile

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequent	Viral infection, respiratory infection, pneumonia, urinary tract infection, otitis media

MedDRA system organ class	**Frequency**	**Adverse reactions**
Blood and lymphatic system disorders	Frequent	Leukopenia
Immune system disorders	Less frequent	Allergic reactions
Metabolism and nutrition disorders	Frequent	Anorexia, increased appetite
	Less frequent	Hyperglycaemia or hypoglycaemia (most often seen in diabetic patients)
Psychiatric disorders	Frequent	Confusion, depression, emotional lability, nervousness, thinking abnormal, hostility, anxiety
	Less frequent	Agitation
Nervous system disorders	Frequent	Ataxia, dizziness, somnolence amnesia, abnormal coordination, dysarthria, insomnia, headache, nystagmus, tremor
	Less frequent	Hypokinesia, mental impairment, loss of consciousness
Eye disorders	Frequent	Visual disturbances such as amblyopia, diplopia
Ear and labyrinth disorders	Frequent	Vertigo
Cardiac disorders	Less frequent	Palpitations
Vascular disorders	Frequent	Vasodilation, hypertension
Respiratory, thoracic and mediastinal disorders	Frequent	Coughing, pharyngitis, rhinitis bronchitis, dyspnoea

MedDRA system organ class	Frequency	Adverse reactions
	Less frequent	Respiratory depression
Gastrointestinal disorders	Frequent	Abdominal pain, constipation, dental abnormalities, diarrhoea, dyspepsia, dry mouth or throat, nausea and/or vomiting, gingivitis, flatulence
	Less frequent	Dysphagia
Skin and subcutaneous tissue disorders	Frequent	Acne, pruritus, rash, facial oedema, purpura
Musculoskeletal and connective tissue disorders	Frequent	Back pain, myalgia, twitching, arthralgia
Reproductive system and breast disorders	Frequent	Impotence
General disorders and administration site conditions	Frequent	Fatigue, Fever, peripheral oedema, abnormal gait, pain, malaise, flu syndrome
	Less frequent	Generalised oedema
Investigations	Frequent	WBC (white blood cell count) decreased, weight increase
	Less frequent	Elevated liver function tests and bilirubin
Injury, poisoning and procedural complications	Frequent	Abrasion, fracture
	Less frequent	Fall

Postmarking experience

The following additional adverse reactions have been reported:

MedDRA system organ class	**Adverse reactions**
Blood and lymphatic system disorders	Thrombocytopenia
Immune system disorders	Hypersensitivity syndrome (systemic reaction that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, anaphylaxis
Metabolism and nutrition disorders	Hyponatraemia
Psychiatric disorders	Hallucinations
Nervous system disorders	Other movement disorders (e.g. dyskinesia, dystonia, choreoathetosis)
Ear and labyrinth disorders	Tinnitus
Gastrointestinal disorders	Pancreatitis
Hepatobiliary disorders	Hepatitis, jaundice
Skin and subcutaneous tissue disorders	Steven-Johnsons syndrome, angioedema, erythema multiforme, alopecia, rash with eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders	Myoclonus, rhabdomyolysis
Renal and urinary disorder	Acute renal failure, incontinence
Reproductive system and breast disorders	Breast hypertrophy, gynaecomastia, sexual dysfunction (changes in libido, ejaculation disorders, anorgasmia)
General disorders and administration site disorders	Withdrawal reactions (anxiety, nausea, pains, insomnia, sweating), chest pain
Investigations	Blood creatinine phosphokinase increased

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

Acute oral overdoses of gabapentin up to 49 grams have been reported. In these cases, double vision, slurred speech, drowsiness, lethargy, loss of consciousness and diarrhoea were observed. All patients recovered with supportive care.

Overdoses of gabapentin, in particularly with CNS depressant medicines, may result in coma. Gabapentin can be removed by haemodialysis. Although haemodialysis is usually not required, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Other antiepileptics ATC code: N03AX12

Pharmacological classification: A2.5 Central nervous system depressants -Anticonvulsants, including anti – epileptics

The precise mechanisms by which gabapentin produces its antiepileptic actions is unknown. Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but has no effect on GABA binding, uptake, or degradation.

Studies have shown that gabapentin binds with high-affinity to the α2δ subunit of voltage-activated calcium channels; however, the relationship of this binding to the therapeutic effects of gabapentin is unknown.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, peak plasma concentrations of gabapentin are observed after 2 to 3 hours. Gabapentin bioavailability is not dose proportional, i.e., as dose is increased, bioavailability decreases. Absolute bioavailability of a 300 mg capsule of gabapentin is approximately 55 %. Food has no effect on gabapentin pharmacokinetics.

Distribution

Less than 3 % of gabapentin circulates bound to plasma protein. And has a volume of distribution of 57,7 litres. In patients with epilepsy, steady-state pre-dose (C_{min}) concentrations of gabapentin in cerebrospinal fluid ranged from 7 – 35 % of the corresponding plasma concentrations.

Elimination

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

Gabapentin elimination half-life 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 from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Linearity/non-linearity

Gabapentin bioavailability is not dose proportional, i.e., as dose is increased, bioavailability decreases.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PRASEN 100, 300 & 400 contains the following excipients:

Corn (Maze) Starch

Magnesium Stearate

Mannitol

Talc

Capsule shell for **PRASEN 100**:

Gelatin

Purified water

Titanium Dioxide (E171)

Capsule shell for **PRASEN 300**:

Gelatin

Iron oxide yellow (E172)

Purified water

Titanium Dioxide (E171)

Capsule shell for **PRASEN 400**:

FD&C Blue #1 (E133)

FD&C Yellow #6 (E110)

Gelatin

Purified water

Titanium Dioxide (E171)

Printing ink for **PRASEN 100, 300 & 400**:

The imprinting ink Green Tek SB 4027 contains shellac, iron oxide yellow (E172) & FD&C Blue #1 Aluminium Lake (E133).

The imprinting ink Blue Tek SB 6018 contains shellac and FD&C Blue #2 Aluminium Lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years. Store at or below 25 °C.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

A white high-density polypropylene (HDPE) container. The container closure system is child resistant. Each HDPE container contains 100 or 500 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Strides Pharma SA (Pty) Ltd

106 16th Road

Building 2

Midrand, 1685

8 REGISTRATION NUMBER(S)

PRASEN 100 - 540154.151

PRASEN 300 - 540155.152

PRASEN 400 - 540156.153

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT