1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of medicinal product

Gabapentin Capsules USP 300/400 mg

2. Composition:

Each capsule contains.
Gabapentin USP ..... 300 mg
Excipients ..... Q.S.
Approved Colour used in empty capsule shells.

Each capsule contains.
Gabapentin USP ..... 400 mg
Excipients ..... Q.S.
Approved Colour used in empty capsule shells.

3. Pharmaceutical Form:

Capsule

4. Clinical Particulars

4.1 Indication

Epilepsy
Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above.
Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

4.2 Posology and Administration

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.
The effective dose of gabapentin in children aged 6 years and older is 25 to 35 mg/kg/day.
For oral use.
Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid-intake (e.g. a glass of water).

4.3 Contraindication

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special Warning & precautions for use

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and Drug rash with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with gabapentin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, gabapentin should be withdrawn immediately and an alternative treatment considered (as appropriate).
If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of gabapentin, treatment with gabapentin must not be restarted in this patient at any time.

Anaphylaxis
Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis.

Suicidal ideation and behaviour
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Cases of suicidal ideation and behaviour have been observed in patients treated with gabapentin in the post-marketing experience.
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. Discontinuation of gabapentin treatment should be considered in case of suicidal ideation and behaviour.

Acute pancreatits
If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered.

Seizures
Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus.
As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.
Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

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 gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin, or concomitant treatment with CNS depressants including opioids, should be reduced appropriately.
Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression. In a population-based, observational, nested case-control study of opioid users, co prescription of opioids and gabapentin was associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio [aOR], 1.49 [95% CI, 1.18 to 1.88, $p<0.001$]).

Respiratory depression
Gabapentin 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.

Misuse, Abuse potential and dependence
Gabapentin can cause drug dependence, which may occur at therapeutic doses. Cases of abuse and misuse have been reported. Patients with a history of substance abuse may be at higher risk for gabapentin misuse, abuse and dependence, and gabapentin should be used with caution in such patients. Before prescribing gabapentin, the patient's risk of misuse, abuse or dependence should be carefully evaluated.
Patients treated with gabapentin should be monitored for symptoms of gabapentin misuse, abuse or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

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

feeling abnormal, dizziness, and malaise. The occurrence of withdrawal symptoms following discontinuation of gabapentin may indicate drug dependence. The patient should be informed about this at the start of the treatment. If gabapentin should be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication.

4.5 Interaction with other medicinal products and other forms of interaction

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

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 gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

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

Co-administration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

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

4.6 Fertility, Pregnancy and lactation

Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the antiepileptics used.

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother.

4.7 Effects on ability to drive and use machines

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms.
Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

4.8 Undesirable effects

Common: Anorexia, Emotional lability,
Uncommon: Nervousness, Nausea, Diarrhoea, Abdominal pain, Skin rash,
Rare: Bone marrow depression, Convulsions, Retinopathy and changes in pigmentation and visual field defect, Vomiting, Cardiomyopathy, which may result in cardiac failure, in some cases with fatal outcome. T-top deviations in ECG.
Unknown: Anaemia and aplastic anaemia, Agranulocytosis
White blood cell count decreased Thrombocytopenia Porphyria aggravated, Hypoglycaemia, Dizziness , Anxiety , Suicidal behaviour ,Psychosis ,Depression , Hallucinations , Agitation , Confusion , Delusions , Mania ,Sleep disorders, Allergic reactions such as urticaria and angioedema Bronchospasm

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 grams.

Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimise toxicity from overdoses.

Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.

Although gabapentin can be removed by haemodialysis, based on prior experience it is not usually required. However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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

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 GABAA or GABAB receptor 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 α 2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α 2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than α 2δ.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours.

Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Biotransformation

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced.

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.

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children> 5 years of age are similar to those in adults when dosed on a mg/kg basis.

In a pharmacokinetic study in 24 healthy paediatric subjects aged between 1 month and 48 months, an approximately 30% lower exposure (AUC), lower Cmax and

higher clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

5.3 Preclinical Safety Data
No Applicable

6. Pharmaceutical Parameters
6.1 List of excipients
Dummy granules
Colloidal silicon dioxide
Purified talc
Magnesium stearate
Capsule Size "0" green /Yellow

6.2 Incompatibilities
Not Applicable

6.3 Shelf Life
24 months

6.4 Special precaution for Storage

Do not store above 30°C.

6.5 Special Precautions for Disposal and other handling
Not Applicable

7. Applicant Information

Wings Pharm Africa Ltd

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10. Manufacturer

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