PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

NUBACAP 25 hard gelatine capsule

NUBACAP 75 hard gelatine capsule

NUBACAP 150 hard gelatine capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NUBACAP 25: Each capsule contains 25 mg pregabalin.

NUBACAP 75: Each capsule contains 75 mg pregabalin.

NUBACAP 150: Each capsule contains 150 mg pregabalin.

NUBACAP is sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

NUBACAP 25: Opaque white, size “4” hard gelatine capsules, radially imprinted with ‘A’ on cap and ‘140’ on body with black ink, filled with white to off-white powder.

NUBACAP 75: Opaque white and opaque orange, size “4” hard gelatine capsules, radially imprinted with ‘A’ on cap and ‘142’ on body with black ink, filled with white to off-white powder.

NUBACAP 150: Opaque white, size “2” hard gelatine capsules, radially imprinted with ‘A’ on cap and ‘144’ on body with black ink, filled with white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NUBACAP is indicated for the treatment of adult patients with neuropathic pain due to Herpes zoster infections and diabetes.

4.2 Posology and method of administration

Posology:

The recommended starting dose for NUBACAP is 75 mg twice daily (150 mg/day), with or without food.

Based on individual patient response and tolerability, the dose may be increased to 150 mg twice daily after an interval of 3 to 7 days.

If NUBACAP has to be discontinued, it is recommended this should be done gradually over a minimum of one (1) week.

Special Populations

Patients with renal impairment:

NUBACAP is eliminated from the systemic circulation primarily by renal excretion as unchanged medicine. As NUBACAP clearance is directly proportional to creatinine clearance (see section 5.2, *Special patient groups*, *Renal impairment*), dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CL_{cr}), as indicated in Table 1 and determined using the following formula:

$$CL_{cr}\ (mL/min) = \frac{(140 - age) \times Wt\ (kg)}{0{,}82 \times serum\ creatinine\ (\mu mol/L)}$$

*For females multiply the CL_{cr} by 0,85.

NUBACAP is removed effectively from plasma by haemodialysis (50 % of

NUBACAP in 4 hours). For patients receiving haemodialysis, the [PRODUCT NAME] daily dose should be adjusted based on renal function. In addition to the daily dose, a supplementary dose should be given immediately following every 4-hour haemodialysis treatment (see Table 1).

Table 1: NUBACAP dosage adjustment based on renal function

Creatinine clearance (CL_{cr}) (mL/min)	Total NUBACAP daily dose*		Dose regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	300	Two divided doses
30 - 60	75	150	Once daily **or** Two divided doses
15 - 30	25 - 50	75	Once daily **or** Two divided doses
< 15	25	25 - 50	Once daily
Supplementary dosage following haemodialysis (mg)			
	25	50	Single dose[+]

*Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

[+]Supplementary dose is a single additional dose.

Patients with hepatic impairment:

No dosage adjustment is required for patients with hepatic impairment (see section 5.2, *Special patient groups*, *Hepatic impairment*).

Elderly patients (over 65 years of age):

No dosage adjustment is necessary for elderly patients unless their renal function is compromised (see Table 1).

Paediatric population:

The safety and effectiveness of NUBACAP in patients below the age of 18 years, with neuropathic pain, have not been established.

Method of administration

NUBACAP is given orally with or without food.

4.3 Contraindications

Hypersensitivity to pregabalin or to any of the inactive ingredients of NUBACAP (see sections 2 and 6.1).

4.4 Special warnings and precautions for use

Hypersensitivity reactions:

There have been post-marketing reports of hypersensitivity reactions, including cases of angioedema and urticaria. NUBACAP should be discontinued immediately if symptoms of angioedema, such as facial, perioral or upper airway swelling occur (see section 4.8).

Severe cutaneous adverse reactions (SCARs):

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported in association with pregabalin 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, NUBACAP should be withdrawn immediately and an alternative treatment considered (as appropriate).

Diabetic patients:

NUBACAP may increase weight gain. Diabetic patients who gain weight on NUBACAP treatment may need to adjust the dose of hypoglycaemic medicines.

Congestive heart failure:

There have been post-marketing reports of congestive heart failure or deterioration of heart failure in some patients receiving NUBACAP. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral oedema and cardiovascular complications such as hypertension or congestive heart failure. NUBACAP should be used with caution in patients with congestive heart failure (see section 4.8).

Renal failure:

Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, improved renal function following discontinuation or dose reduction of NUBACAP has been reported (see section 4.8). Renal failure has occurred.

Dizziness, somnolence, loss of consciousness and mental impairment:

NUBACAP treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in elderly patients. There have been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of NUBACAP (see section 4.8).

Antidepressants:

When NUBACAP is used in combination with antidepressants, respiratory failure has occurred.

Withdrawal symptoms:

After discontinuation of short-term and long-term treatment with NUBACAP, withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsions, hyperhidrosis and dizziness, suggestive of physical dependence (see section 4.8). Patients should be informed about this at the start of the treatment.

Convulsions, including status epilepticus and grand mal convulsions, may occur during NUBACAP use or shortly after discontinuing NUBACAP.

Concerning discontinuation of long-term treatment of NUBACAP, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.

Vision-related effects:

There have been post-marketing reports of visual adverse reactions including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of NUBACAP may result in resolution or improvement of these visual symptoms.

Additional adverse effects found in patients with central neuropathic pain due to spinal cord injury:

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, central nervous system adverse reactions and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medicinal products (e.g. anti-spasticity medicines) needed for this condition. This should

be considered when prescribing pregabalin in this condition.

Suicidal ideation and behaviour:

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic medicines in several indications. 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.

Reduced lower gastrointestinal tract function:

There are post-marketing reports of events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) when NUBACAP was co-administered with medicines that have the potential to produce constipation, such as opioid analgesics. When NUBACAP and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and the elderly).

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 NUBACAP misuse, abuse or dependence (development of tolerance, dose escalation, substance-seeking behaviour have been reported).

Encephalopathy:

Cases of encephalopathy have been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

Respiratory depression:

There have been reports of severe respiratory depression in relation to NUBACAP use. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly may be at higher risk of experiencing this severe adverse reaction. Dose adjustments may be necessary in these patients (see section 4.2).

4.5 Interaction with other medicines and other forms of interaction

Since NUBACAP is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (< 2 % of a dose recovered in urine as metabolites), does not inhibit substance metabolism *in vitro*, and is not bound to plasma proteins, [PRODUCT NAME] is unlikely to produce, or be subject to, pharmacokinetic interactions.

Accordingly, *in vivo* studies indicated no clinically relevant pharmacokinetic interactions between NUBACAP and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. In addition, population pharmacokinetic analysis indicated that the 3 commonly used medicine classes, oral antidiabetics, diuretics and insulin, and the commonly used anti-epileptic medicines, phenytoin, carbamazepine, valproic acid, lamotrigine, phenobarbitone, tiagabine, and topiramate had no clinically significant effect on pregabalin clearance. Similarly, these analyses indicated that NUBACAP had no clinically significant effect on the clearance of phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate and phenobarbitone.

Co-administration of NUBACAP with the oral contraceptives norethisterone and/or ethinylestradiol does not influence the steady-state pharmacokinetics of either medicine.

Multiple oral doses of NUBACAP co-administered with oxycodone, lorazepam or ethanol did not result in clinically important effects on respiration. NUBACAP appears to be additive in the impairment of cognitive and gross motor function caused by

oxycodone. NUBACAP may potentiate the effects of ethanol and lorazepam. In post-marketing experience, there are reports of respiratory failure and coma in patients taking NUBACAP and other central nervous system (CNS) depressant medicines.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no adequate data on the use of NUBACAP in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown. Therefore, NUBACAP should not be used during pregnancy.

Lactation:

It is not known if NUBACAP is excreted into the breast milk of humans; however, it is present in the milk of rats. Therefore, breastfeeding is not recommended.

4.7 Effects on ability to drive and use machines

NUBACAP frequently causes dizziness and somnolence (see section 4.8).
Caution is advised before driving a vehicle or operating machinery until it is established that the ability to perform such activities is not affected.

4.8 Undesirable effects

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Less frequent	Infection, nasopharyngitis.
Blood and the lymphatic system disorders	Less frequent	Neutropenia.
Immune system disorders	Less frequent	Hypersensitivity reaction, Stevens-Johnson syndrome, angioedema, allergic reaction.

Metabolism and nutrition disorders	Frequent Less frequent	Increased appetite. Anorexia, hypoglycaemia.
Psychiatric disorders	Frequent Less frequent	Euphoric mood, confusion, irritability, disorientation, insomnia. Depersonalisation, anorgasmia, restlessness, depression, agitation, mood swings, depressed mood, aggression, word finding difficulty, hallucinations, abnormal dreams, panic attack, apathy, disinhibition, elevated mood, nervousness.
Nervous system disorders	Frequent <

	Less frequent	Visual disturbance, dry eye, eye swelling, visual acuity reduced, eye pain, asthenopia, increased lacrimation, photopsia, eye irritation, mydriasis, vision loss, keratitis, oscillopsia, altered visual depth perception, peripheral vision loss, strabismus, visual brightness, visual field defect, nystagmus.
Ear and labyrinth disorders	Frequent Less frequent	Vertigo. Hyperacusis.
Cardiac disorders	Less frequent	Tachycardia, first degree atrioventricular block, sinus tachycardia, sinus dysrhythmia, sinus bradycardia, congestive heart failure, chest tightness, chest pain, QT prolongation.
Vascular disorders	Less frequent	Flushing, hot flushes, hypotension, peripheral coldness, hypertension.
Respiratory, thoracic and mediastinal disorders	Less frequent Frequency unknown	Dyspnoea, nasal dryness, nasopharyngitis, cough, nasal congestion, epistaxis, rhinitis, snoring, throat tightness, flu symptoms, bronchitis, pulmonary oedema. Respiratory depression
Gastrointestinal disorders	Frequent	Dry mouth, constipation, vomiting, flatulence, nausea, diarrhoea, abdominal

		distension.
	Less frequent	Salivary hypersecretion, gastro-oesophageal reflux disease, oral hypaesthesia, ascites, dysphagia, pancreatitis, swollen tongue.
Hepatobiliary disorders	Less frequent	Elevated liver enzymes, jaundice, hepatic failure, hepatitis.
Skin and subcutaneous tissue disorders	Less frequent	Sweating, papular rash, cold sweat, urticaria, hyperhidrosis, pruritus.
Musculoskeletal, connective tissue and bone disorders	Less frequent	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness, cervical spasm, neck pain, rhabdomyolysis.
Renal and urinary disorders	Less frequent	Dysuria, urinary incontinence, oliguria, renal failure, urinary retention.
Reproductive system and breast disorders	Frequent Less frequent	Erectile dysfunction, decreased libido. Delayed ejaculation, sexual dysfunction, increased libido, amenorrhoea, breast pain, breast discharge, dysmenorrhoea, breast hypertrophy, gynaecomastia.
General disorders and administrative site conditions	Frequent Less frequent	Fatigue, peripheral oedema, facial oedema, oedema, abnormal gait, accidental injury. Asthenia, fall, thirst, exacerbated pain, anasarca, pyrexia, rigors.
Investigations	Frequent Less frequent	Increased weight. Increased alanine aminotransferase,

		increased blood creatine phosphokinase, increased aspartate aminotransferase, decreased platelet count, increased blood glucose, increased blood creatinine, decreased blood potassium, decreased weight, decreased white blood cell count.

Reporting of suspected adverse reactions:

Reporting of 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

Symptoms:

The most commonly reported adverse events observed when NUBACAP was taken in overdose included affective disorder, somnolence, confusion, depression, agitation, restlessness, seizures and coma.

Treatment:

Treatment of NUBACAP overdose should be symptomatic and supportive and may include haemodialysis if necessary (see section 4.2, *Patients with renal impairment*).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

A 2.5 Central nervous system depressants: Anticonvulsants, including anti-epileptics.

Pharmacotherapeutic group: Anti-epileptics, other anti-epileptics.

ATC code: N03AX16

Mechanism of action

Pregabalin is a gamma-aminobutyric acid (GABA) analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid).

Pregabalin binds, *in vitro*, to an auxiliary subunit (α_2-ð protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin. In animal models it was shown that binding of pregabalin to the α_2-ð site is required for analgesic activity. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

Pregabalin does not interact with either $GABA_A$ or $GABA_B$ receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of GABA uptake or degradation. Pregabalin prevents pain-related behaviours of neuropathic and post-surgical pain, including hyperalgesia and allodynia.

5.2 Pharmacokinetic Properties

Absorption:

Pregabalin is absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be ≥ 90 % and is independent of dose. Following repeated administration, steady state is achieved within 24 to 48 hours. The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25 – 30 % and a delay in t_{max} to approximately 2,5 hours. However, administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption.

Distribution:

In animals, pregabalin crosses the blood brain barrier and the placenta, and is present in breast milk. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0,56 L/kg. Pregabalin is not bound to plasma proteins.

Metabolism:

Pregabalin undergoes negligible metabolism. Following a dose of radio-labelled pregabalin, approximately 98 % of the radioactivity recovered in the urine was unchanged pregabalin. The *N*-methylated derivative of pregabalin, the major metabolite of pregabalin found in urine, accounted for 0,9 % of the dose. There is no indication of racemisation of pregabalin *S*-enantiomer to the *R*-enantiomer.

Elimination:

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged medicine. Pregabalin mean elimination half-life is 6,3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see *Special patient groups*, Renal impairment). Dosage adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see section 4.2, Table 1).

Linearity/non-linearity:

Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (< 20 %). Multiple dose pharmacokinetics are predictable from single-dose data. Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.

Special patient groups:

Gender:

Gender does not have a clinically significant influence on the plasma concentrations of

pregabalin.

Renal impairment:

Pregabalin clearance is directly proportional to creatinine clearance. In addition, pregabalin is effectively removed from plasma by haemodialysis (following a 4 hour haemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50 %). Because renal elimination is the major elimination pathway, dosage reduction in patients with renal impairment and dosage supplementation following haemodialysis are necessary (see section 4.2, Table 1).

Hepatic impairment:

No specific pharmacokinetic studies were carried out in patients with impaired liver function. Since pregabalin does not undergo significant metabolism and is excreted predominantly as unchanged medicine in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

Elderly (over 65 years of age):

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function (see section 4.2, Table 1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Pregelatinised starch

Talc.

Capsule shell

Gelatine

Titanium dioxide.

The capsule shell of NUBACAP 75 also contains iron oxide red (colourant).

Printing ink

Black iron oxide

Shellac.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

NUBACAP 25: 24 months

NUBACAP 75: 36 months

NUBACAP 150: 36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep the blister strips in the carton until required for use.

Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

NUBACAP 25, 75 and 150 are packed in blister strips of clear PVC/aluminium

and packed into an outer cartons.

Pack size: 10, 14, 56, 60 or 100 capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd.

Block B, Arena Office Park

272 West Avenue

Centurion

0157

South Africa

8. REGISTRATION NUMBERS

NUBACAP 25: 48/2.5/1339

NUBACAP 75: 48/2.5/1340

NUBACAP 150: 48/2.5/1341

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 November 2019

10. DATE OF REVISION OF THE TEXT

To be allocated.

NUBACAP 25: Namibia Reg No.: 18/2.5/0005	NS3
NUBACAP 75: Namibia Reg No.: 18/2.5/0006	NS3
NUBACAP 150: Namibia Reg No.:18/2.5/0007	NS3