PROFESSIONAL INFORMATION FOR NUBACAP 25 / 75 / 150

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

NUBACAP 25 hard gelatine capsule

NUBACAP 75 hard gelatine capsule

NUBACAP 150 hard gelatine capsule

COMPOSITION

Active ingredient:

NUBACAP 25: Each capsule contains 25 mg pregabalin.

NUBACAP 75: Each capsule contains 75 mg pregabalin.

NUBACAP 150: Each capsule contains 150 mg pregabalin.

Inactive ingredients:

Pregelatinised starch and talc.

The capsule shell contains gelatine and titanium dioxide, and is imprinted with black printing ink (consisting of black iron oxide and shellac).

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

Sugar free.

CATEGORY AND CLASS

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

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

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.

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 **DOSAGE AND**

DIRECTIONS FOR USE, 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 **DOSAGE AND DIRECTIONS FOR USE**, 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 **DOSAGE AND DIRECTIONS FOR USE**, Table 1).

INDICATIONS

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

and diabetes.

CONTRAINDICATIONS

Hypersensitivity to pregabalin or to any of the inactive ingredients of **NUBACAP** (see **COMPOSITION**).

WARNINGS AND SPECIAL PRECAUTIONS

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 **SIDE EFFECTS**).

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 **SIDE EFFECTS**).

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 **SIDE EFFECTS**). 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 **SIDE EFFECTS**).

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 **SIDE EFFECTS**). 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.

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.

Effects on ability to drive and use machines:

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

INTERACTIONS

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, **NUBACAP** 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.

HUMAN REPRODUCTION

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.

DOSAGE AND DIRECTIONS FOR USE

The safety and effectiveness of **NUBACAP** in patients below the age of 18 years, with neuropathic pain, have not been established. **NUBACAP** is given orally with or without food.

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.

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 **Pharmacokinetic properties,** *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 **NUBACAP** 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 **Pharmacokinetic properties,** *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).

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: Increased appetite.

Less frequent: Anorexia, hypoglycaemia.

Psychiatric disorders:

Frequent: Euphoric mood, confusion, irritability, disorientation, insomnia.

Less frequent: 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: Dizziness, somnolence, headache, ataxia, attention disorder, abnormal coordination, memory impairment, tremor, dysarthria, paraesthesia, abnormal thinking, amnesia, sedation, balance disorder, lethargy.

Less frequent: Cognitive disorder, hypoaesthesia, speech disorder, myoclonus, hyporeflexia, dyskinesia, psychomotor hyperactivity, postural dizziness, hyperaesthesia, ageusia, burning sensation, intention tremor, stupor, syncope, loss of consciousness, mental impairment, reversible paralysis, malaise, convulsions, hypokinesia, parosmia, dysgraphia, myasthenia, neuropathy.

Eye disorders:

Frequent: Blurred vision, diplopia.

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: Vertigo.

Less frequent: 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: Dyspnoea, nasal dryness, nasopharyngitis, cough, nasal congestion, epistaxis, rhinitis, snoring, throat tightness, flu symptoms, bronchitis, pulmonary oedema.

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: Erectile dysfunction, decreased libido.

Less frequent: Delayed ejaculation, sexual dysfunction, increased libido, amenorrhoea, breast pain, breast discharge, dysmenorrhoea, breast hypertrophy, gynaecomastia.

General disorders and administrative site conditions:

Frequent: Fatigue, peripheral oedema, facial oedema, oedema, abnormal gait, accidental injury.

Less frequent: Asthenia, fall, thirst, exacerbated pain, anasarca, pyrexia, rigors.

Investigations:

Frequent: Increased weight.

Less frequent: 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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 **DOSAGE AND DIRECTIONS FOR USE**, **Patients with renal impairment**).

IDENTIFICATION

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.

PRESENTATION

NUBACAP 25, 75 and **150** are packed in blister strips of clear PVC/aluminium and packed into an outer carton containing 10, 14, 56, 60 or 100 capsules each.

STORAGE INSTRUCTIONS

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.

REGISTRATION NUMBERS

NUBACAP 25: 48/2.5/1339

NUBACAP 75: 48/2.5/1340

NUBACAP 150: 48/2.5/1341

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

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