Professional Information for Medicines for Human Use

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

NEUCAPOR 25 mg

NEUCAPOR 75 mg

NEUCAPOR 150 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

NEUCAPOR 25 mg:

Each capsule contains 25 mg of pregabalin.

Sugar free.

NEUCAPOR 75 mg:

Each capsule contains 75 mg of pregabalin.

Sugar free.

NEUCAPOR 150 mg:

Each capsule contains 150 mg of pregabalin.

Sugar free.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

NEUCAPOR 25 mg:

Capsules, hard. White cap / White body, size ‘5’ hard gelatine capsule shells, imprinted with “Z” on cap and “10” on body with black ink contains white to off-white granular powder.

The dimensions of the size ‘5’ capsules are as follows:

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Length:

6.2±0.4 mm for the cap,

9.3±0.4 mm length for the body

Width:

4.91±0.03 mm for the cap

4.65±0.03 mm for the body

NEUCAPOR 75 mg:

Capsules, hard. Orange cap / white body, size '4' hard gelatine capsule shells, imprinted with "Z" on cap and "12" on body with black ink contains white to off-white granular powder.

The dimensions of the size '4' capsules are as follows:

Length:

7.2±0.4 mm for the cap,

12.2±0.4 mm length for the body

Width:

5.33±0.03 mm for the cap

5.06±0.03 mm for the body

NEUCAPOR 150 mg:

Capsules, hard. White cap / white body, size '2' hard gelatine capsule shells, imprinted with "Z" on cap and "14" on body with black ink contains white to off-white granular powder.

The dimensions of the size '2' capsules are as follows:

Length:

9±0.4 mm for the cap,

15.2±0.4 mm length for the body

Width:

6.37±0.03 mm for the cap

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6.08±0.03 mm for the body

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Neuropathic Pain:

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

4.2. Posology and method of administration

Posology

The recommended starting dose for **NEUCAPOR** 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.

In accordance with current clinical practice, if **NEUCAPOR** has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Patients with renal impairment:

NEUCAPOR is eliminated from the systemic circulation primarily by renal excretion as unchanged pregabalin. As **NEUCAPOR** clearance is directly proportional to creatinine clearance (see section 5.2– Renal impairment), dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

$$\text{CLcr (mL/min)} = \frac{(140 - \text{age}) \times \text{Weight (kg)}}{0{,}82 \times \text{serum creatinine (µmol/L)}}$$

* For females multiply the CLcr by 0,85

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NEUCAPOR is removed effectively from plasma by haemodialysis (50 % of drug in 4 hours).

For patients receiving haemodialysis, the **NEUCAPOR** 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: Pregabalin Dose Adjustment Based on Renal Function

Creatinine Clearance (CLcr) (mL/min)	**Total NEUCAPOR Daily Dose***		**Dose Regimen**
	Starting dose (mg/day)	**Maximum dose (mg/day)**	
≥ 60	150	300	BD
30 – 60	75	150	OD or BD
15 – 30	25 – 50	75	OD or BD
< 15	25	25 – 50	OD
Supplementary dosage following haemodialysis (mg)			
	25	50	Single dose+

BD = Two divided doses

OD = Once daily

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

+ Supplementary dose is a single additional dose.

<u>Use in patients with hepatic impairment:</u>

No dosage adjustment is required for patients with hepatic impairment (see section 5.2– Hepatic impairment).

The safety and effectiveness of **NEUCAPOR** in patients below the age of 18 years with neuropathic pain has not been established.

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Use in the elderly (over 65 years of age):

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

Method of administration

NEUCAPOR is given orally with or without food

4.3. Contraindications

NEUCAPOR is contraindicated in patients who are hypersensitive to the active ingredient pregabalin or to any of excipients listed in 6.1

4.4. Special warnings and precautions for use

Diabetic patients

Diabetic patients who gain weight on **NEUCAPOR** treatment may need to adjust hypoglycaemic medicinal products.

Hypersensitivity reactions

There have been reports of hypersensitivity reactions, including cases of angioedema. Pregabalin should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur.

Dizziness, somnolence, loss of consciousness, confusion and mental impairment

Pregabalin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have also 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 the medicinal product.

Vision-related effects Visual adverse reactions have been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of **NEUCAPOR** may result in resolution or improvement of these visual symptoms.
Renal failure Cases of renal failure have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.
Withdrawal symptoms After discontinuation of short-term and long-term treatment with pregabalin, as contained in **NEUCAPOR,** withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment. Convulsions, including status epilepticus and grand mal convulsions, may occur during pregabalin use or shortly after discontinuing pregabalin. Concerning discontinuation of long-term treatment of **NEUCAPOR**, data suggest that the incidence and severity of withdrawal symptoms may be dose-related.
Congestive heart failure Congestive heart failure have been reported in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. **NEUCAPOR** should be used with caution in these patients. Discontinuation of **NEUCAPOR** may resolve the reaction.

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Suicidal ideation and behaviour Suicidal ideation and behaviour have been reported in patients treated with gabapentinoids, such as pregabalin in **NEUCAPOR**, in several indications. Therefore, patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Patients and caregivers should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.
Reduced lower gastrointestinal tract function Events related to reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) have been reported when pregabalin as contained in **NEUCAPOR**, was co-administered with medicines that have the potential to produce constipation, such as opioid analgesics. When **NEUCAPOR** and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and elderly).
Concomitant use with opioids Caution is advised when prescribing **NEUCAPOR** concomitantly with opioids due to risk of CNS depression (see section 4.5). In a case control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone (adjusted odds ratio [aOR], 1.68 [95% CI, 1.19 - 2.36]). This increased risk was observed at low doses of pregabalin (≤ 300 mg, aOR 1.52 [95% CI, 1.04 - 2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, aOR 2.51 [95% CI 1.24 - 5.06]).
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 **NEUCAPOR** misuse, abuse or dependence (development of tolerance, dose escalation, drug-seeking behaviour have been reported).

Encephalopathy

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

4.5. Interaction with other medicines and other forms of interaction

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

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between **NEUCAPOR** 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 **NEUCAPOR** had no clinically significant effect on the clearance of phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate and phenobarbitone.

Co-administration of **NEUCAPOR** with the oral contraceptives norethisterone and/or ethinyl oestradiol does not influence the steady-state pharmacokinetics of either medicine.

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

There are reports of respiratory failure and coma in patients taking **NEUCAPOR** and other central nervous system depressant medicines.

Interactions and the elderly

No specific pharmacodynamic interaction studies were conducted in elderly volunteers.

Interaction studies have only been performed in adults.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

Pregnancy

There are no adequate data from the use of pregabalin in pregnant women.

Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

NEUCAPOR should not be used during pregnancy.

Breastfeeding

Pregabalin is excreted into human milk. The effect of pregabalin on newborns/infants is unknown. Therefore, breastfeeding is not recommended during treatment with **NEUCAPOR**.

Fertility

There are no clinical data on the effects of pregabalin on female fertility.

4.7. Effects on ability to drive and use machines

NEUCAPOR frequently causes dizziness and somnolence. Head and body injuries and road traffic incidents have also been reported with pregabalin as contained in **NEUCAPOR** Therefore, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicine affects their ability to perform these activities.

4.8. Undesirable effects

Some cases of hypersensitivity reactions (including angioedema) have been reported with **NEUCAPOR.**

The most common adverse effects associated with **NEUCAPOR** are dizziness, somnolence, loss of consciousness, confusion and mental impairment, with the elderly population the most prone to these adverse effects. Visual adverse reactions (loss of vision and visual blurring) have also been reported but these symptoms have been known to resolve or improve upon discontinuing treatment with **NEUCAPOR** (see section 4.4).

The most commonly reported adverse reactions are tabulated below.

The frequencies are defined as follows:

Frequent ≡ more frequent',

Less frequent ≡ 'single reports', 'isolated reports', or not frequent '

"Frequency not known" or "frequency unknown" When no frequency data are available for a specific ADR, the statement added, with justification provided in the cover letter for the lack of information and providing the reference sources consulted.

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Tabulated list of adverse reactions

System Organ Class	**Adverse drug reactions**
Infections and infestations	
Frequent	Nasopharyngitis
Blood and lymphatic system disorders	
Less frequent	Neutropenia
Immune system disorders	
Less frequent	Hypersensitivity Angioedema, allergic reaction
Metabolism and nutrition disorders	
Frequent	Appetite increased
Less frequent	Anorexia, hypoglycaemia
Psychiatric disorders	
Frequent	Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
Less frequent	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, insomnia, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy, disinhibition, elevated mood
Frequency unknown	Suicidal ideation and behaviour
Nervous system disorders	
Frequent	Dizziness, somnolence, headache, ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypaesthesia, sedation, balance disorder, lethargy

Less frequent	Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder, visual field defect, hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise, convulsions, parosmia, hypokinesia, dysgraphia	
Eye disorders		
Frequent	Vision blurred, diplopia	
Less frequent	visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, dry eye, lacrimation increased, eye irritation , photopsia, vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness, peripheral vision loss,	
Ear and labyrinth disorders		
Frequent	Vertigo	
Less frequent	Hyperacusis	
Cardiac disorders		
Less frequent	Tachycardia, congestive heart failure, atrioventricular block first degree, sinus bradycardia , QT prolongation, sinus tachycardia, sinus dysrhythmia	
Vascular disorders		
Less frequent	Hot flushes, flushing, hypotension, hypertension, peripheral coldness	
Respiratory, thoracic and mediastinal disorders		

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Less frequent	Dyspnoea, nasal dryness epistaxis, nasopharyngitis cough, nasal congestion, rhinitis, snoring, pulmonary oedema, throat tightness
Gastrointestinal disorders	
Frequent	Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth
Less frequent	Gastroesophageal reflux disease, salivary hypersecretion, hypaesthesia oral, ascites, pancreatitis, swollen tongue, dysphagia
Hepatobiliary disorders	
Less frequent	Elevated liver enzymes, jaundice, hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Less frequent	Rash papular, sweating, urticaria, hyperhidrosis, pruritus, Stevens Johnson syndrome, cold sweat
Musculoskeletal and connective tissue disorders	
Frequent	Muscle cramp, back pain, pain in limb, cervical spasm
Less frequent	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness, arthralgia, rhabdomyolysis
Renal and urinary disorders	
Less frequent	Urinary incontinence, dysuria, renal failure, oliguria, urinary retention
Reproductive system and breast disorders	
Frequent	Erectile dysfunction

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Less frequent	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, amenorrhoea, breast discharge, breast enlargement, breast pain , gynaecomastia
General disorders and administration site conditions	
Frequent	Oedema peripheral, oedema, gait abnormal, feeling drunk, feeling abnormal, fatigue
Less frequent	Generalised oedema, face oedema, fall, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Frequent	Weight increased
Less frequent	Alanine aminotransferase increased, aspartate aminotransferase increased, Blood creatine phosphokinase increased, platelet count decreased, white blood cell count decreased, blood glucose increased, blood creatinine increased, blood potassium decreased, weight decreased

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Medicine Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose

In the post marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported.

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In rare occasions, cases of coma have been reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 2.5 Central nervous system depressants - Anticonvulsants; including antiepileptics.

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). It binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin. In animal models it was shown that binding of pregabalin to the α2-δ site is required for analgesic activity.

5.2. Pharmacokinetic properties

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, and patients with chronic pain.

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

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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 preclinical studies, pregabalin has been shown to cross the blood brain barrier in mice, rats, and monkeys. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. 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.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabelled 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. In preclinical studies, there was 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 drug.

Pregabalin mean elimination half-life is 6.3 hours. Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance (see section 5.2 Renal impairment).

Dose 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.

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, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is 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 drug in the urine, impaired liver function would not be expected to significantly alter pregabalin plasma concentrations.

Elderly

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).

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

The other ingredients of **NEUCAPOR** are:

- Maize starch Ph.Eur
- Talc Ph.Eur
- Empty hard gelatine capsule shell

NEUCAPOR 25 mg:

1. Constituents of the capsule:

The capsule shell contains:

- Gelatine,
- Sodium lauryl sulphate
- Water
- Titanium dioxide (C.I. No: 77891 and E No: E 171).

2. Constituents of the printing ink:

The printing ink contains:

- Shellac
- Dehydrated Alcohol
- Isopropyl alcohol
- Butyl Alcohol
- Propylene Glycol
- Strong Ammonia solution
- Black Iron oxide (C.I. No: 77499)
- Potassium hydroxide

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- Purified water

NEUCAPOR 75 mg:

1. Constituents of the capsule:

The capsule shell contains:

- Gelatine,
- Sodium lauryl sulphate
- Water
- Titanium dioxide (C.I. No: 77891 and E No: E 171)
- Iron oxide red (E No: 172)

2. Constituents of the printing ink:

The printing ink contains:

- Shellac
- Dehydrated Alcohol
- Isopropyl alcohol
- Butyl Alcohol
- Propylene Glycol
- Strong Ammonia solution
- Black Iron oxide (C.I. No: 77499)
- Potassium hydroxide
- Purified water

NEUCAPOR 150 mg:

1. Constituents of the capsule:

The capsule shell contains:

- Gelatine,
- Sodium lauryl sulphate

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- Water
- Titanium dioxide (C.I. No: 77891 and E No: E 171)

2. Constituents of the printing ink:

The printing ink contains:

- Shellac
- Dehydrated Alcohol
- Isopropyl alcohol
- Butyl Alcohol
- Propylene Glycol
- Strong Ammonia solution
- Black Iron oxide (C.I. No: 77499)
- Potassium hydroxide
- Purified water

6.2. Incompatibilities

Not applicable

6.3. Shelf life

2 years

6.4. Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep HDPE containers tightly closed.

Keep all medicines out of the reach and sight of children

6.5. Nature and contents of container

NEUCAPOR 25 mg

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1) Blister Pack:

Capsules are packed in an aluminium foil blister pack.

Pack size: 60's – Each carton contains 6 blisters of 10 capsules each.

2) HDPE Pack:

Capsules are packed in white opaque round 40 mL HDPE bottle.

Pack size: 60's – One HDPE container contains 60 capsules.

NEUCAPOR 75 mg

1) Blister Pack:

Capsules are packed in an aluminium foil blister pack.

Pack size: 60's – Each carton contains 6 blisters of 10 capsules each.

2) HDPE Pack:

Capsules are packed in white opaque round 60 mL HDPE bottle **Pack size**: 60's – One HDPE container contains 60 capsules.

NEUCAPOR 150 mg

1) Blister Pack:

Capsules are packed in an aluminium foil blister pack.

Pack size: 60's – Each carton contains 6 blisters of 10 capsules each.

2) HDPE Pack:

Capsules are packed in white opaque round 75 mL HDPE bottle. **Pack size**: 60's – One HDPE container contains 60 capsules.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements for the disposal and handling of

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NEUCAPOR.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8. REGISTRATION NUMBER
NEUCAPOR 25 mg 48/2.5/1070
NEUCAPOR 75 mg 48/2.5/1071
NEUCAPOR 150 mg 48/2.5/1072

9. DATE OF FIRST AUTHORISATION
08 December 2020

10. DATE OF REVISION OF TEXT