SCHEDULING STATUS

S5

1. NAME OF MEDICINE:

NEUPROG 25 Capsules

NEUPROG 75 Capsules

NEUPROG 150 Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

NEUPROG 25

Each **NEUPROG** 25 capsule contains 25 mg pregabalin

NEUPROG 75

Each **NEUPROG** 75 capsule contains 75 mg pregabalin

NEUPROG 150

Each **NEUPROG** 150 capsule contains 150 mg pregabalin

For the full list of excipients, see **section 6.1**

3. PHARMACEUTICAL FORM:

Hard gelatin capsules

NEUPROG 25: Opaque white/ Opaque white size “4” Hard gelatin capsules radially imprinted with ‘A’ on cap and ‘140’ on body with black ink filled with white to off white powder.

NEUPROG 75: Opaque white/ Orange Opaque size “4” Hard gelatin capsules radially imprinted with ‘A’ on cap and ‘142’ on body with black ink filled with white to off white powder.

NEUPROG 150: Opaque white/ Opaque white size “2” Hard gelatin 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

Neuropathic pain:

NEUPROG 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

The recommended starting dose for **NEUPROG** 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 **NEUPROG** has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Special Populations

Renal impairment

NEUPROG is eliminated from the systemic circulation primarily by renal excretion as unchanged medicine. As **NEUPROG** clearance is directly proportional to creatinine clearance (see section 5.2), dose 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:

$$\text{CLcr (mL/min)} = \frac{(140 - \text{age}) \times \text{Wt (kg)}}{}$$

0,82 x Serum creatinine (µmol/L)

*For females multiply the CLcr by 0,85

NEUPROG is removed effectively from plasma by haemodialysis (50% of medicine in 4 hours). For patients receiving haemodialysis, the **NEUPROG** 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. NEUPROG dosage adjustment based on renal function

Creatinine clearance (CLcr) (mL/min)	Total **NEUPROG** 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

Hepatic impairment

No dose adjustment is required for patients with hepatic impairment (see section 5.2).

Elderly

No dosage adjustment is necessary for elderly patients unless their renal function is compromised,

see Table 1.

Paediatric population

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

Method of administration

NEUPROG may be taken with or without food.

NEUPROG is for oral use only.

4.3 Contraindications

Hypersensitivity to the pregabalin or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Diabetic patients

In accordance with current clinical practice, some diabetic patients who gain weight on **NEUPROG** treatment may need to adjust hypoglycaemic medicines.

Hypersensitivity reactions

There have been reports in the postmarketing experience of hypersensitivity reactions, including cases of angioedema. **NEUPROG** should be discontinued immediately if symptoms of angioedema, such as facial, perioral, or upper airway swelling occur (see section 4.8).

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

NEUPROG 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 (see section 4.8).

Vision-related effects

In controlled trials, a higher proportion of patients treated with pregabalin reported blurred vision than did patients treated with placebo which resolved in a majority of cases with continued dosing. In the clinical studies where ophthalmologic testing was conducted, the incidence of visual acuity reduction and visual field changes was greater in pregabalin -treated patients than in placebo-treated patients; the incidence of fundoscopic changes was greater in placebo-treated patients (see section 5.1).

In the post-marketing experience, visual adverse reactions have also been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of **NEUPROG** may result in resolution or improvement of these visual symptoms

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 pregabalin has been reported (see section 4.8). Renal failure has occurred.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with pregabalin 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. Patients should be advised to immediately report any symptoms of depression and or suicidal ideation.

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

Congestive heart failure

There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. **NEUPROG** should be used in caution in these patients with congestive heart failure.

Treatment of 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 medicines (e.g. anti-spasticity **medicines**) needed for this condition. This should be considered when prescribing **NEUPROG** 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 pregabalin was co-administered with medications that have the potential to produce constipation, such as opioid analgesics. When **NEUPROG** 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 **NEUPROG** 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 **NEUPROG** 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 medicine metabolism *in vitro*, and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.

***In vivo* studies and population pharmacokinetic analysis**

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Population pharmacokinetic

analysis indicated that the 3 commonly used drug classes, oral antidiabetics, diuretics, insulin, and the commonly used anti-epileptic drugs, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Oral contraceptives, norethisterone and/or ethinyl oestradiol

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

Central nervous system influencing medicines

NEUPROG may potentiate the effects of ethanol and lorazepam. In controlled clinical trials, multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. In the postmarketing experience, there are reports of respiratory failure, coma and deaths in patients taking pregabalin and opioids and/or other central nervous system (CNS) depressant medicines. **NEUPROG** appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

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 childbearing potential.

Pregnancy

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

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

NEUPROG should not be used during pregnancy.

Breast-feeding

It is not known if NEUPROG is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breastfeeding is not recommended. The effect of **NEUPROG** on newborns/infants is unknown.

Fertility

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

4.7 Effects on the ability to drive and use machines

NEUPROG may cause dizziness and somnolence and therefore may influence the ability to drive or operate machines. Patients are advised not to drive, operate complex machinery, or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity.

Adverse reactions

Below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (frequent, (≥1/10); (≥1/100 to <1/10); less frequent (≥1/1,000 to <1/100); (≥1/10,000 to <1/1,000); (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions listed may also be associated with the underlying disease and/or concomitant medicines.

Additional reactions reported from post-marketing experience are included in italics in the list below.

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, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy, disinhibition

Nervous system disorders

Frequent: Dizziness, somnolence, headache, ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, 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, hyporeflexia, hyperaesthesia, burning sensation, ageusia, *malaise, convulsions, parosmia, hypokinesia, dysgraphia*

Eye disorders

Frequent: Vision blurred, diplopia

Less frequent: Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation, *Vision loss, keratitis*, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness

Ear and labyrinth disorders

Frequent: Vertigo

Less frequent: Hyperacusis

Cardiac disorders

Less frequent: Tachycardia, atrioventricular block first degree, sinus bradycardia, *congestive heart failure, QT prolongation, sinus tachycardia, sinus arrhythmia*

Vascular disorders

Less frequent: Hypotension, hypertension, hot flushes, flushing, peripheral coldness

Respiratory, thoracic, and mediastinal disorders

Less frequent: Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness, pulmonary oedema, throat tightness

Gastrointestinal disorders

Frequent: Vomiting, *nausea*, constipation, *diarrhoea*, flatulence, abdominal distension, dry mouth

Less frequent: Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia 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, urticaria, hyperhidrosis, *pruritus, Stevens Johnson syndrome*, cold sweat

Musculoskeletal and connective tissue disorders

Frequent: Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm

Less frequent: Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness, rhabdomyolysis

Renal and urinary disorders

Less frequent: Urinary incontinence, dysuria, Renal failure, oliguria, *urinary retention*

Reproductive system and breast disorders

Frequent: Erectile dysfunction

Less frequent: Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain, Amenorrhoea, breast discharge, breast enlargement, *gynaecomastia*

General disorders and administration site conditions

Frequent: Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue

Less frequent: Generalised oedema, *face oedema*, chest tightness, pain, pyrexia, thirst, chills, asthenia

Investigations

Frequent: Weight increased

Less frequent: Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased, White blood cell count decreased

Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

Description of selected adverse reactions

After discontinuation of short-term and long-term treatment with **NEUPROG** withdrawal symptoms have been observed in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment. Concerning discontinuation of long-term treatment of pregabalin, data suggest that the incidence and severity of withdrawal symptoms may be dose related.

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of 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: hppts://www.sahpra.or.za/Publications/Index/8

4.9 Overdose

Symptoms

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

Seizures were also reported.

In rare occasions, cases of coma have been reported.

Management

Treatment of **NEUPROG** overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2).

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

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

Anti-epileptics, other anti-epileptics; ATC code: N03AX16.

Mechanism of action

Pregabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin. Two lines of evidence indicate that binding of pregabalin to the α2-δ site is required for analgesic activity in animal models: (1) Studies with the inactive R-enantiomer and other structural derivatives of pregabalin and (2) Studies of pregabalin in mutant mice with defective drug binding to the α2-δ protein. 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 in animal models of neuropathic and post-surgical pain, including hyperalgesia and allodynia

5.2 Pharmacokinetic properties

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic medicines 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 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.

Biotransforamtion

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).

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.

Gender

Clinical trials indicate that 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 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).

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 (over 65 years of age)

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decrease 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

NEUPROG 25, 75, and 150 mg

Black iron oxide, gelatin, potassium hydroxide, pregelatinized starch, propylene glycol, shellac, talc, titanium dioxide.

6.2 Incompatibilities

None

6.3 Shelf life

24 months

6.4 Nature and contents of container

NEUPROG 25, 75 and 150 mg is available in:

Blisters of PVC (forming foil) & Aluminium lidding foil containing 14, 56, 60 & 100 capsules. Such blisters are packed into a carton along with a patient information leaflet. Not all pack sizes may be marketed.

6.5 Special precautions for storage

Do not store above 30 ^{o}C

6.6 Special precautions for disposal and other handling

No special requirements

7. Holder of certificate of registration

Innovata Pharmaceuticals

Crownwood Office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

South Africa

8. Registration numbers

9. Date of first authorisation/Renewal of the authorisation

10. Date of revision of the text

REFERENCES:

Reference 1

Pfizer Laboratories (Pty) Ltd

Lyrica

Final approved PI

Reference 2

SmPC Pregabalin Consilient 25mg hard capsules

Consilient Health Limited,

5th Floor, Beaux Lane House,

Mercer Street Lower,

Dublin 2,

Ireland

Date of first authorisation/renewal of the authorisation

Date of first authorisation: 23/12/2014

Date of latest renewal: 04/08/2019

Date of revision of the text

27/07/2020