novugen

Novugab

Pregabalin

1. NAME OF THE MEDICINAL PRODUCT

Novugab 50 mg Capsules, Novugab 75 mg Capsules, and Novugab 150 mg Capsules.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Novugab 50 mg Capsules
Each capsule contains 50 mg of pregabalin.
Novugab 75 mg Capsules
Each capsule contains 75 mg of pregabalin.
Novugab 150 mg Capsules
Each capsule contains 150 mg of pregabalin.

3. PHARMACEUTICAL FORM

Novugab 50 mg Capsules
White to off-white powder filled in size '4' hard gelatin capsule, printed with 'P 50' on white body and 'N' on white cap in black ink.

Novugab 75 mg Capsules
White to off-white powder filled in size '4' hard gelatin capsule, printed with 'P 75' on white body and 'N' on red cap in black ink.

Novugab 150 mg Capsules
White to off-white powder filled in size '2' hard gelatin capsule, printed with 'P 150' on white body and 'N' on white cap in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain
Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy
Pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

Generalised anxiety disorder
Pregabalin is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

Fibromyalgia
Pregabalin is indicated for the management of fibromyalgia.

4.2 Posology and method of administration

The dose range is 150 to 600 mg per day given in either two or three divided doses.
Pregabalin may be taken with or without food. Novugab is for oral use only.

Neuropathic pain
Pregabalin treatment can be started at a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after an interval of 3 to 7 days, and if needed, to a maximum dose of 600 mg per day after an additional 7-day interval.

Fibromyalgia
The usual dose range for most patients is 300 to 450 mg per day given in two divided doses. Some patients may derive additional benefit at 600 mg per day. Dosing should begin at 75 mg two times a day (150 mg/day) and may be increased to 150 mg two times a day (300 mg/day) within 1 week based on efficacy and tolerability. Patients who do not experience sufficient benefit with 300 mg/day may be further increased to 225 mg two times a day (450 mg/day). If needed, in some patients, based on individual response and tolerability, the dose may be increased to maximum dosage of 600 mg/day after an additional week.

Epilepsy
Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. The maximum dosage of 600 mg per day may be achieved after an additional week.

Generalised anxiety disorder
The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.
Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week.

Discontinuation of pregabalin
If pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Patients with renal impairment
Dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr) (see Section **5.2 Pharmacokinetic properties,** Pharmacokinetics in special patient groups, *Renal impairment*), as indicated in Table 1 determined using the following formula:

$$CL_{cr}\ (mL/min) = \left[\frac{[140 - age\ (years)]\ x\ weight\ (kg)}{72\ x\ serum\ creatinine\ (mg/dL)}\right]\ (\text{x } 0.85 \text{ for female patients})$$

For patients receiving hemodialysis, the pregabalin 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 Dosage Adjustment Based on Renal Function

	Total Pregabalin Daily Dose*		
Creatinine Clearance (CLcr) (mL/min)	Starting Dose (mg/day)	Maximum Dose (mg/day)	Dose Regimen
≥60	150	600	BID or TID
≥30 - <60	75	300	BID or TID
≥15 - <30	25 –50	150	QD or BID
<15	25	75	QD
Supplementary dosage following haemodialysis (mg)			
	25	100	Single dose

TID = Three divided doses.
BID = Two divided doses.
QD = Single daily 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.

Use in patients with hepatic impairment
No dosage adjustment is required for patients with hepatic impairment (see Section **5.2 Pharmacokinetic properties,** Pharmacokinetics in special patient groups, *Hepatic impairment*).

Use in children and adolescents (12 to 17 years of age)

The safety and effectiveness of pregabalin in pediatric patients below the age of 12 years and adolescents has not been established.

The use in children is not recommended.

Use in the elderly (over 65 years of age)

Elderly patients may require a dose reduction of pregabalin due to decreased renal function (see Section **5.2 Pharmacokinetic properties,** Pharmacokinetics in special patient groups, *Elderly (over 65 of age).*

4.3 Contraindications

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

4.4 Special warnings and precautions for use

4.4.1 Angioedema

Exercise caution when prescribing pregabalin to patients who have had a previous episode of angioedema. In addition, patients who are taking other drugs associated with angioedema (e.g., angiotensin converting enzyme inhibitors [ACE-inhibitors]) may be at increased risk of developing angioedema.

4.4.2 Hypersensitivity

Adverse reactions included skin redness, blisters, hives, rash, dyspnea, and wheezing. Discontinue pregabalin immediately in patients with these symptoms.

4.4.3 Withdrawal of Antiepileptic Drugs (AEDs)

As with all AEDs, withdraw pregabalin gradually to minimize the potential of increased seizure frequency in patients with seizure disorders. If pregabalin is discontinued, taper the drug gradually over a minimum of 1 week.

4.4.4 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including pregabalin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with any AED for any indication for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.
Anyone considering prescribing pregabalin or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.
Inform patients, their caregivers, and families that pregabalin and other AEDs increase the risk of suicidal thoughts and behavior and advise them of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Report behaviors of concern immediately to healthcare providers.

4.4.5 Peripheral Edema

Pregabalin treatment may cause peripheral edema.
As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, exercise caution when co-administering pregabalin and these agents.
Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, exercise caution when using pregabalin in these patients.

4.4.6 Dizziness and Somnolence

Pregabalin may cause dizziness and somnolence. Inform patients that pregabalin-related dizziness and somnolence may impair their ability to perform tasks such as driving or operating machinery and could increase the occurrence of accidental injury (fall) in the elderly population.
Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, carefully evaluate patients for history of drug abuse and observe them for signs of pregabalin misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

4.4.7 Weight Gain

Pregabalin treatment may cause weight gain. Some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycemic medications.

4.4.8 Abrupt or Rapid Discontinuation

Following abrupt or rapid 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. 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.
There are insufficient data for the withdrawal of concomitant antiepileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.

4.4.9 Ophthalmological Effects

Inform patients to notify their physician if changes in vision occur. If visual disturbance persists, consider further assessment. Consider more frequent assessment for patients who are already routinely monitored for ocular conditions. Discontinuation of pregabalin may result in resolution or improvement of these visual symptoms.

4.4.10 Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Instruct patients to promptly report unexplained muscle pain, tenderness, or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Discontinue treatment with pregabalin if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

4.4.11 Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count,

4.4.12 PR Interval Prolongation

Pregabalin treatment was associated with PR interval prolongation.

4.4.13 Others

Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, improved renal failure following discontinuation or dose reduction of pregabalin has been reported.

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 pregabalin 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.

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 medicinal products (e.g., anti-spasticity agents) needed for this condition. This should be considered when prescribing pregabalin in this condition.

4.5 Interaction with other medicinal products 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 and is not bound to plasma proteins, it is unlikely to produce, or be subject to, pharmacokinetic interactions.
Co-administration of pregabalin with the oral contraceptives norethisterone and/or ethinyl estradiol does not influence the steady-state pharmacokinetics of either substance. Pregabalin may potentiate the effects of ethanol and lorazepam. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.
In the post marketing experience, there are reports of respiratory failure, coma and deaths in patients taking Pregabalin and opioids and/or other central nervous system (CNS) depressant medicinal products.

4.6 Fertility, pregnancy and lactation

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

The potential risk for humans is unknown. Therefore, pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Effective contraception must be used in women of child bearing potential.

Lactation
Pregabalin is excreted in the milk of lactating women (see section **5.2 Pharmacokinetic properties**). As the safety of pregabalin in infants is not known, breast-feeding is not recommended during treatment with pregabalin. A decision must be made whether to discontinue breast-feeding or to discontinue from pregabalin therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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

4.8 Undesirable effects
The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

The following adverse drug reactions were reported:

System Organ Class	Adverse drug reactions
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropaenia
Immune system disorders	
Uncommon	Hypersensitivity
Rare	Angioedema, allergic reaction
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia, hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, irritability, disorientation, insomnia, libido decreased
Uncommon	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition
Nervous system disorders	
Very Common	Dizziness, somnolence, headache
Common	Ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy
Uncommon	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
Rare	Convulsions, parosmia, hypokinesia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, visual acuity reduced, eye pain, asthenopia, photopsia, dry eye, lacrimation increased, eye irritation
Rare	Vision loss, keratitis, oscillopsia, altered visual depth perception, mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Uncommon	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia, atrioventricular block first degree, sinus bradycardia, congestive heart failure
Rare	QT prolongation, sinus tachycardia, sinus arrhythmia
Vascular disorders	
Uncommon	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness
Rare	Pulmonary oedema, throat tightness
Not known	Respiratory depression
Gastrointestinal disorders	
Common	Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth
Uncommon	Gastrooesophageal reflux disease, salivary hypersecretion, hypoaesthesia oral
Rare	Ascites, pancreatitis, swollen tongue, dysphagia
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Rash papular, urticaria, hyperhidrosis, pruritus
Rare	Stevens Johnson syndrome, cold sweat
Musculoskeletal and connective tissue disorders	
Common	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
Uncommon	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness
Rare	Rhabdomyolysis
Renal and urinary disorders	
Uncommon	Urinary incontinence, dysuria
Rare	Renal failure, oliguria, urinary retention
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, ejaculation delayed, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, gynaecomastia
General disorders and administration site conditions	
Common	Oedema peripheral, oedema, gait abnormal, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations	
Common	Weight increased
Uncommon	Blood creatine phosphokinase increased, blood glucose increased, platelet count decreased, blood creatinine increased, blood potassium decreased, weight decreased
Rare	White blood cell count decreased
* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).	

4.9 Overdose
In overdoses up to 15 g, no unexpected adverse reactions were reported.
The most commonly reported adverse events observed when pregabalin was taken in overdose included affective disorder, somnolence, confusional state, depression, agitation and restlessness. Seizures were also reported.
Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see Section 4.2 Posology and method of administration, Table 1).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antiepileptics, ATC code: N03A (proposed).
The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5- methylhexanoic acid).

Mechanism of action
Pregabalin binds to an auxiliary subunit (γ2-δ protein) of voltage-gated calcium channels in the central nervous system.

5.2 Pharmacokinetic properties
Pregabalin steady-state pharmacokinetics are similar in healthy volunteers, patients with epilepsy receiving anti-epileptic drugs, and patients with chronic pain.

Absorption
Pregabalin is rapidly 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 Cmax 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 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 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.

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 Pharmacokinetic properties,** Pharmacokinetics in special patient groups, *Renal impairment*).
Dosage adjustment in patients with reduced renal function or undergoing hemodialysis is necessary (see Section **4 Posology and method of administration**, Table 1).

Linearity/Non-linearity
Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter -subject pharmacokinetic variability for pregabalin is low (<20%). Therefore, there is no need for routine monitoring of plasma concentrations of pregabalin.

Pharmacokinetics in 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 hemodialysis (following a 4-hour hemodialysis 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 hemodialysis is necessary (see Section **4.2 Posology and method of administration**, Table 1).

Hepatic impairment
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 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 Posology and method of administration**, Table 1).

Breast-feeding mothers
Lactation had little to no influence on pregabalin pharmacokinetics. Pregabalin was excreted into breast milk with average steady-state concentrations approximately 76% of those in maternal plasma. The estimated average daily infant dose of pregabalin from breast milk (assuming mean milk consumption of 150mL/kg/day) was 0.31 mg/kg/day, which on a mg/kg basis would be approximately 7% of the maternal dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Capsule Content:
Pregelatinized Starch
Talc

Capsule Shell:
Gelatin

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Please refer outer carton for expiry date.

6.4 Special precautions for storage
Store below 30°C. Keep in a cool, dry place away from sunlight.

6.5 Nature and contents of container
Blisters containing 10's (1 x 10's), 14's (1 x 14's), 28's (2 x 14's), 30's (3 x 10's), 56's (4 x 14's), 60's (6 x 10's), 100's (10 x 10's), 112's (8 x 14's) or 120's (12 x 10's) hard gelatin capsules in the outer box.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product.
No special requirements.

6.7 Route of administration
Oral

6.8 Source/ Origin of gelatin
Bovine

6.9 Product Registration Holder
Novugen Pharma Sdn. Bhd.
No.3, Jalan Jururancang U1/21,
Hicom Glenmarie Industrial Park,
40150 Shah Alam, Selangor, Malaysia.

6.10 Manufactured by:
Novugen Pharma Sdn. Bhd. No.27,
Jalan Lengkuk Teknologi 2,
Taman Teknologi Enstek Fasa 1, 71760,
Bandar Baru Enstek, Negeri Sembilan, Malaysia.

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