# SUMMARY OF PRODUCT CHARACTERISTICS

# 1 NAME OF THE MEDICINAL PRODUCT

Pregabalin Northumbria 50 mg hard capsules

# 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule of Pregabalin 50 mg contains 50 mg of pregabalin.

For the full list of excipients, see section 6.1.

# 3 PHARMACEUTICAL FORM

Hard capsules
50 mg
White cap and body, size 3 capsule, imprinted with "50" on the body with black ink

# 4 CLINICAL PARTICULARS

## 4.1 Therapeutic indications

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

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

*Generalised Anxiety Disorder*
Pregabalin hard capsules is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

## 4.2 Posology and method of administration

Prior to starting treatment with pregabalin, a discussion should be held with patients to put in place a strategy for ending treatment with pregabalin in order to minimise the risk of dependence, addiction and drug withdrawal syndrome (see section 4.4).
Treatment should be given for the shortest possible duration. If this medicine is being used for the treatment of epilepsy this medicine should be used for as long as the prescriber considers it necessary.

Posology
The dose range is 150 to 600 mg per day given in either two or three divided doses.

*Neuropathic pain*

Pregabalin treatment can be started at a dose of 150 mg per day given as two or three divided doses.
Based on individual patient response and tolerability, the dose 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.

*Epilepsy*
Pregabalin treatment can be started with a dose of 150 mg per day given as two or three divided doses.
Based on individual patient response and tolerability, the dose may be increased to 300 mg per day after 1 week. The maximum dose 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 dose may be increased to 300 mg per day after 1 week. Following an additional week the dose may be increased to 450 mg per day. The maximum dose of 600 mg per day may be achieved after an additional week.

*Discontinuation of pregabalin*
In accordance with current clinical practice, if pregabalin has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see sections 4.4 and 4.8).

*Renal impairment*
Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug.
As pregabalin 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 ($CL_{cr}$), as indicated in Table 1 determined using the following formula:

$$CLcr\left(\frac{ml}{min}\right) = [\quad \frac{1.23\ [140\ -\ \text{age (years)}]\text{x weight (kg)}}{\text{(kg) serum creatinine (^mol/l)}} \quad ](\text{x } 0.85 \text{ for female patients})$$

Pregabalin is removed effectively from plasma by haemodialysis (50% of drug in 4 hours). For patients receiving haemodialysis, 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 dose adjustment based on renal function**

| Creatinine clearance (CLcr) (mL/min) | Total pregabalin daily dose * | | Dose regimen |
|---|---|---|---|
| | Starting dose (mg/day) | Maximum dose (mg/day) | |
| ≥ 60 | 150 | 600 | BID or TID |
| ≥30 - <60 | 75 | 300 | BID or TID |
| ≥15 - <30 | 25 – 50 | 150 | Once Daily or BID |
| < 15 | 25 | 75 | Once Daily |
| Supplementary dosage following haemodialysis (mg) | | | |
| | 25 | 100 | Single dose[+] |

TID = Three divided doses
BID = Two divided doses
***** 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).

*Paediatric population*
The safety and efficacy of Pregabalin hard capsules in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Currently available data are described in section 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

*Elderly*
Elderly patients may require a dose reduction of pregabalin due to a decreased renal function (see section 5.2).

Method of administration
Pregabalin hard capsules may be taken with or without food.
Pregabalin hard capsules is for oral use only.

## 4.3 Contraindications

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

## 4.4 Special warnings and precautions for use

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be life-threatening or fatal, have been reported rarely in association with pregabalin treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, pregabalin should be withdrawn immediately and an alternative treatment considered (as appropriate).

*Diabetic patients*
In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicinal products.

*Hypersensitivity reactions*

There have been reports in the postmarketing experience 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*
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 pregabalin 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 of concomitant anti-epileptic medicinal products*
There are insufficient data for the withdrawal of concomitant anti-epileptic medicinal products, once seizure control with pregabalin in the add-on situation has been reached, in order to reach monotherapy on pregabalin.

*Congestive heart failure*
There have been post-marketing reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. Pregabalin should be used with caution in these patients. Discontinuation of pregabalin may resolve the reaction.

*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.

*Suicidal ideation and behaviour*
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled studies of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Cases of suicidal ideation and behaviour have been observed in patients treated with pregabalin in the postmarketing experience (see section 4.8). An epidemiological study using a self-controlled study design (comparing treatment periods

with non-treatment periods within an individual) showed evidence of an increased risk of new onset of suicidal behaviour and death by suicide in patients treated with pregabalin.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Patients should be monitored for signs of suicidal ideation and behaviour and appropriate treatment should be considered. Discontinuation of pregabalin treatment should be considered in case of suicidal ideation and behaviour.

*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 pregabalin 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 pregabalin 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]).

*Drug dependence, tolerance and potential for abuse*

Drug addiction comprises behavioural, cognitive and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use and possible tolerance or physical dependence. Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, which manifests as withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug. Addiction and dependence are related but distinct presentations and in discussing these themes, terminology that apportion blame to the individual should be avoided.

For all patients, prolonged use of this product may lead to drug dependence and addiction but can occur with short-term use at recommended therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of drug misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of symptom control as initially experienced.

Patients may also supplement their treatment with additional medications to achieve the same effect. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.

The clinical need for treatment with pregabalin should be reviewed regularly, with frequent assessments of patients being undertaken during the course of their treatment.

*Drug withdrawal syndrome*
Prior to starting treatment with pregabalin, a discussion should be held with patients to explain the risk of dependence, addiction, and drug withdrawal syndrome. A withdrawal strategy for ending treatment with pregabalin should also be put in place with the patient before starting treatment (there may be exceptions to this in specific clinical situations such as symptom management in end of life palliative care, and for use in epilepsy).
Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take in excess of weeks or months. Patients should be informed of this when the medication is first prescribed.
The reduction schedule for a patient should be tailored to the individual and should be modified to allow intolerable withdrawal symptoms to improve before making the next reduction. If using a published withdrawal schedule, apply it flexibly to accommodate the person's preferences, changes to their circumstances and the response to dose reductions. Reduce the dose by a fixed amount at each decrement, unless clinical risk is such that rapid withdrawal is needed.
If a patient develops withdrawal reactions, consider pausing the taper or increasing the dosage to the previous tapered dosage level.
If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

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

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

*Women of childbearing potential/Contraception*

Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment (see section 4.6).

## 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 *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 oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

*Oral contraceptives, norethisterone and/or ethinyl oestradiol*

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

*Central nervous system influencing medical products*
Pregabalin may potentiate the effects of ethanol and lorazepam.
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 medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone.

*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*
Women of childbearing potential have to use effective contraception during treatment (see section 4.4).

*Pregnancy*
Studies in animals have shown reproductive toxicity (see section 5.3).

Pregabalin has been shown to cross the placenta in rats (see section 5.2). Pregabalin may cross the human placenta.

*Major congenital malformations*

Data from a Nordic observational study of more than 2700 pregnancies exposed to pregabalin in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the paediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%).

The risk of MCM among the paediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35)), and compared to population exposed to lamotrigine (1.29 (1.01–1.65)) or to duloxetine (1.39 (1.07–1.82)).
The analyses on specific malformations showed higher risks for malformations of the nervous system, the eye, orofacial clefts, urinary malformations and genital malformations, but numbers were small and estimates imprecise.

Pregabalin hard capsules should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

*Breast-feeding*
Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

In a clinical trial to assess the effect of pregabalin on sperm motility, healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment, there were no effects on sperm motility.

A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and developmental effects. The clinical relevance of these findings is unknown (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Pregabalin hard capsules may have minor or moderate influence on the ability to drive and use machines. Pregabalin hard capsules 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 medicinal product affects their ability to perform these activities.

## 4.8 Undesirable effects

The pregabalin clinical programme involved over 8900 patients exposed to pregabalin, of whom over 5600 were in double-blind placebo controlled trials. The most commonly reported adverse reactions were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from pregabalin treatment groups were dizziness and somnolence.

In the table below all adverse reactions, which occurred at an incidence greater than placebo and in more than one patient, are listed by class and frequency (very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (< 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 medicinal products.

In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse reactions in general, CNS adverse reactions and especially somnolence was increased (see section 4.4).

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

**Table 2. Pregabalin Adverse Drug Reactions**

| **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, suicidal behaviour, suicidal ideation |
| Not known | Drug dependence (see section 4.4) |
| **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, parkinsonism |
| **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, Toxic Epidermal Necrolysis |
| **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).

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed. The following symptoms have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, suicidal ideation, pain**,** hyperhidrosis and dizziness. These symptoms may indicate drug 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 (see sections 4.2 and 4.4).

Paediatric population

The pregabalin safety profile observed in five paediatric studies in patients with partial seizures with or without secondary generalization (12-week efficacy and safety study in patients 4 to 16 years of age, n=295; 14-day efficacy and safety study in patients 1 month to younger than 4 years of age, n=175; pharmacokinetic and tolerability study, n=65; and two 1 year open label follow on safety studies, n=54 and n=431) was similar to that observed in the

adult studies of patients with epilepsy. The most common adverse events observed in the 12-week study with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis. The most common adverse events observed in the 14-day study with pregabalin treatment were somnolence, upper respiratory tract infection, and pyrexia (see sections 4.2, 5.1 and 5.2).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

### 4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

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.

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

Pharmacotherapeutic group: Antiepileptics, other anti-epileptics ATC code: N03AX16

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 ($\alpha_2$-δ protein) of voltage-gated calcium channels in the central nervous system.

Clinical Efficacy and safety

*Neuropathic pain*
Efficacy has been shown in trials in diabetic neuropathy, post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in 10 controlled clinical trials of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In clinical trials up to 12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33% of patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo.

In the controlled clinical trial in central neuropathic pain 22% of the Pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.

*Epilepsy*
Adjunctive Treatment
Pregabalin has been studied in 3 controlled clinical trials of 12 week duration with either BID or TID dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

A reduction in seizure frequency was observed by Week 1.

*Paediatric population*
The efficacy and safety of pregabalin as adjunctive treatment for epilepsy in paediatric patients below the age of 12 and adolescents has not been established. The adverse events observed in a pharmacokinetic and tolerability study that enrolled patients from 3 months to 16 years of age (n=65) with partial onset seizures were similar to those observed in adults. Results of a 12-week placebo-controlled study of 295 paediatric patients aged 4 to 16 years and a 14-day placebo-controlled study of 175 paediatric patients aged 1 month to younger than 4 years of age performed to evaluate the efficacy and safety of pregabalin as adjunctive therapy for the treatment of partial onset seizures and two 1 year open label safety studies in 54 and 431 paediatric patients respectively, from 3 months to 16 years of age with epilepsy indicate that the adverse events of pyrexia and upper respiratory infections were observed more frequently than in adult studies of patients with epilepsy (see sections 4.2, 4.8 and 5.2).

In the 12-week placebo-controlled study, paediatric patients (4 to 16 years of age) were assigned to pregabalin 2.5
mg/kg/day (maximum, 150 mg/day), pregabalin 10/mg/kg/day (maximum, 600 mg/day), or placebo. The percentage of subjects with at least a 50% reduction in partial onset seizures as compared to baseline was 40.6% of subjects treated with pregabalin 10 mg/kg/day (p=0.0068 versus placebo), 29.1% of subjects treated with pregabalin 2.5 mg/kg/day (p=0.2600 versus placebo) and 22.6% of those receiving placebo.

In the 14-day placebo-controlled study, paediatric patients (1 month to younger than 4 years of age) were assigned to pregabalin 7 mg/kg/day, pregabalin 14 mg/kg/day, or placebo. Median 24-hour seizure frequencies at baseline and at the final visit were 4.7 and 3.8 for pregabalin 7 mg/kg/day, 5.4 and 1.4 for pregabalin 14 mg/kg/day, and 2.9 and 2.3 for placebo, respectively. Pregabalin 14 mg/kg/day significantly reduced the log-transformed partial onset seizure frequency versus placebo (p=0.0223); pregabalin 7 mg/kg/day did not show improvement relative to placebo.
In a 12-week placebo-controlled study in subjects with Primary Generalized Tonic-Clonic (PGTC) seizures 219 subjects (aged 5 to 65 years, of which 66 were aged 5 to 16 years) were assigned to pregabalin 5 mg/kg/day (maximum 300 mg/day), 10 mg/kg/day (maximum 600 mg/day) or placebo as adjunctive therapy. The percentage of subjects with at least a 50% reduction in PGTC seizure rate was 41.3%, 38.9% and 41.7% for pregabalin 5 mg/kg/day, pregabalin 10 mg/kg/day and placebo respectively.

Monotherapy (newly diagnosed patients)

Pregabalin has been studied in 1 controlled clinical trial of 56 week duration with BID dosing. Pregabalin did not achieve non-inferiority to lamotrigine based on the 6-month seizure freedom endpoint. Pregabalin and lamotrigine were similarly safe and well tolerated.

*Generalised Anxiety Disorder*
Pregabalin has been studied in 6 controlled trials of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study with a double blind relapse prevention phase of 6 months duration.

Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1.

In controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint. 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. Ophthamologic testing (including visual acuity testing, formal visual field testing and dilated funduscopic examination) was conducted in over 3600 patients within controlled clinical trials. In these patients, visual acuity was reduced in 6.5% of patients treated with pregabalin, and 4.8% of placebo-treated patients. Visual field changes were detected in 12.4% of pregabalin-treated, and 11.7% of placebo-treated patients. Funduscopic changes were observed in 1.7% of pregabalin-treated and 2.1% of placebo-treated patients.

## 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 $C_{max}$ 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.

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.

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 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.

Paediatric population
Pregabalin pharmacokinetics were evaluated in paediatric patients with epilepsy (age groups: 1 to 23 months, 2 to 6 years, 7 to 11 years and 12 to 16 years) at dose levels of 2.5, 5, 10 and 15 mg/kg/day in a pharmacokinetic and tolerability study.

After oral administration of pregabalin in paediatric patients in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.

Pregabalin $C_{max}$ and AUC parameters increased in a linear manner with increasing dose within each age group. The AUC was lower by 30% in paediatric patients below a weight of 30 kg due to an increased body weight adjusted clearance of 43% for these patients in comparison to patients weighing ≥30 kg.

Pregabalin terminal half-life averaged about 3 to 4 hours in paediatric patients up to 6 years of age, and 4 to 6 hours in those 7 years of age and older.

Population pharmacokinetic analysis showed that creatinine clearance was a significant covariate of pregabalin oral clearance, body weight was a significant covariate of pregabalin apparent oral volume of distribution, and these relationships were similar in paediatric and adult patients.

Pregabalin pharmacokinetics in patients younger than 3 months old have not been studied (see sections 4.2, 4.8 and 5.1).

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).

Breast-feeding mothers
The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was evaluated in 10 lactating women who were at least 12 weeks postpartum. 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 infant dose from breast milk (assuming mean milk consumption of 150 ml/kg/day) of women receiving 300 mg/day or the maximum dose of 600 mg/day would be 0.31 or 0.62 mg/kg/day, respectively. These estimated doses are approximately 7% of the total daily maternal dose on a mg/kg basis.

## 5.3 Preclinical safety data

In conventional safety pharmacology studies in animals, pregabalin was well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were observed, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly observed in aged albino rats was seen after long-term exposure to pregabalin at exposures ≥ 5 times the mean human exposure at the maximum recommended clinical dose.

Pregabalin was not teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits occurred only at exposures sufficiently above human exposure. In prenatal/postnatal toxicity studies, pregabalin induced offspring developmental toxicity in rats at exposures >2 times the maximum recommended human exposure.

Adverse effects on fertility in male and female rats were only observed at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reversible and occurred only at exposures sufficiently in excess of therapeutic exposure or were associated with spontaneous degenerative processes in male reproductive organs in the rat. Therefore the effects were considered of little or no clinical relevance.

Pregabalin is not genotoxic based on results of a battery of *in vitro* and *in vivo* tests.

Two-year carcinogenicity studies with pregabalin were conducted in rats and mice. No tumours were observed in rats at exposures up to 24 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day. In mice, no increased incidence of tumours was found at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was observed at higher exposures. The non-genotoxic mechanism of pregabalin-induced tumour formation in mice involves platelet changes and associated endothelial cell proliferation. These platelet changes were not present in rats or in humans based on short term and limited long-term clinical data. There is no evidence to suggest an associated risk to humans.

In juvenile rats the types of toxicity do not differ qualitatively from those observed in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was evidence of CNS clinical signs of hyperactivity and bruxism and some changes in growth (transient body weight gain suppression). Effects on the oestrus cycle were observed at 5-fold the human therapeutic exposure. Reduced acoustic startle response was observed in juvenile rats

1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, this effect was no longer observable.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

*Capsules content:*
Pregelatinized Starch
Mannitol
Talc

*Capsules shell:*
Gelatin
Titanium Dioxide (E171)

*Printing Ink:*
Shellac
Black Iron Oxide (E172)
Propylene Glycol (E1520)
Ammonium Hydroxide (E527)

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

## 6.5 Nature and contents of container

A cardboard box containing the appropriate number of PVC/Aluminium foil blisters containing for:

50 mg 7, 14 or 56, 84 number of hard capsules

Not all pack sizes may be marketed

## 6.6 Special precautions for disposal and other handling

No special requirements for disposal.

# 7 MARKETING AUTHORISATION HOLDER

Northumbria Pharma Limited
NETPark,
Thomas Wright Way,
Sedgefield,
County Durham,
TS21 3FD,
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL GB 48259/0061

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/05/2019

## 10 DATE OF REVISION OF THE TEXT

16/01/2026