

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pragiola 75 mg capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains, 75 mg, of pregabalin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule

Pragiola 75 mg: The capsule body is brownish-yellow, the capsule cap is brownish-yellow. The capsule cap is imprinted with black mark P75. The capsule content is white to off-white powder. Capsule length: 13.8 – 14.8 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Neuropathic pain

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

Epilepsy

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

Generalised Anxiety Disorder

Pragiola is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

4.2 Posology and method of administration

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 should 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:

$$CL_{Cr}(ml/min) = \left[\frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})} \right] (\times 0.85 \text{ for female patients})$$

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 (CL _{Cr}) (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 Pragiola 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 may require a dose reduction of pregabalin due to a decreased renal function (see section 5.2).

Method of administration

Pragiola may be taken with or without food.

Pragiola 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

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 post-marketing 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.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) have been rarely reported in association with pregabalin treatment, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which may be life-threatening or fatal. Upon prescription, patients should be informed of the signs and symptoms and should be closely monitored for skin reactions. If signs and symptoms occur that are suggestive of such reactions, pregabalin should be immediately discontinued and another treatment should be considered (as applicable).

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 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).

As part of 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 impairment

Cases of renal impairment have been reported and in some cases discontinuation of pregabalin did show reversibility of this adverse reaction.

Withdrawal of concomitant antiepileptic medicinal products

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.

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.

Respiratory depression

There have been reports of severe respiratory depression in association with the use of pregabalin. Patients with compromised respiratory function, respiratory or neurological disorder, renal impairment, concomitant use of CNS sedatives and elderly patients may be at a higher risk of developing this severe adverse reaction. Dose adjustments may be required in these patients (see section 4.2).

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. Suicidal ideation and behaviour have been observed in patients treated with pregabalin as part of the post-marketing experience (see section 4.8). An epidemiological study using a self-controlled study design (comparing treatment periods with non-treatment periods in each patient) indicated evidence of an increased risk of new onset of suicidal behaviour and of death by suicide in patients treated with pregabalin.

Patients (and caregivers) should be advised to seek medical advice to identify the first signs of the emergence of suicidal ideation or behaviour. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Pregabalin discontinuation should be considered if suicidal ideation and behaviour occur.

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 should be exercised when prescribing pregabalin concomitantly with opioids due to the risk of CNS depression (see section 4.5). In one case-control study in opioid users, patients who took pregabalin concomitantly with an opioid presented an increased risk of opioid-related death compared to the use of opioids alone (adjusted hazard ratio [aHR], 1.68 [95% CI, 1.19 - 2.36]). This increased risk was observed with small doses of pregabalin (≤ 300 mg, aHR 1.52 [95% CI, 1.04 - 2.22]) and there was a higher risk tendency with high doses of pregabalin (> 300 mg, aHR 2.51, [95% CI, 1.24 – 5.06]).

Misuse, abuse potential or dependence

Pregabalin may cause physical dependence, which may occur at therapeutic doses. Cases of misuse and abuse have been reported. Patients with a history of substance abuse may present a higher risk of pregabalin misuse, abuse and dependence, and pregabalin should be used with caution in these patients. Before prescribing pregabalin, the patient's risk of misuse, abuse or dependence should be carefully assessed.

Patients treated with pregabalin should be monitored for symptoms of pregabalin misuse, abuse or dependence, such as development of tolerance, dose escalation and drug- seeking behaviour.

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. The occurrence of withdrawal symptoms after discontinuation of pregabalin may be suggestive of physical dependence (see section 4.8). The patient should be informed about this at the start of the treatment. If the administration of pregabalin must be discontinued, it is recommended that it be done gradually, over a minimum of 1 week, regardless of indication (see section 4.2).

Seizures, including status epilepticus and grand mal seizures, may occur during pregabalin use or shortly after discontinuing pregabalin.

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

Encephalopathy

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

Women of childbearing potential/Contraception

The use of pregabalin in the first three months of pregnancy may cause major birth defects to the unborn baby. Pregabalin should not be used during pregnancy, except where the therapeutic benefit for the mother clearly outweighs the potential risk for the baby. Women of childbearing potential should use effective birth control during the 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, pharmacokinetic interactions are unlikely.

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 in 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

Effective contraception must be used in women of child bearing potential (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 placenta in humans.

Major birth defects

Data from an observational study conducted in Nordic countries, including more than 2700 pregnancies exposed to pregabalin during the first trimester, showed a higher prevalence of major birth defects (MBDs) in the group of (live or still) births exposed to pregabalin, compared to the group of births without exposure (5.9% compared to 4.1%).

The risk of MBDs in the group of births exposed to pregabalin in the first three months of the pregnancy was slightly higher compared to the risk in the non-exposed population (adjusted hazard ratio and 95% confidence interval: 1.14 (0.96-1.35)) and compared to the lamotrigine- or duloxetine-exposed population (1.39 (1.07-1.82)).

Analyses of specific birth defects showed increased risks of birth defects of the nervous system, eye, orofacial cleft, urinary abnormalities and genital defects, but the number was reduced and the estimates inaccurate.

Pregabalin 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 may have minor or moderate influence on the 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 unless it is known how this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

In a pregabalin clinical programme involving over 8900 patients who were 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.

Tabulated list of adverse reactions

In the table below, all adverse reactions that occur at an incidence greater than placebo and in more than one patient are listed by class and frequency (very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$) and not known [frequency 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. Adverse reactions to pregabalin

System organ class	Adverse drug reactions
Infections and infestations	
Common	Nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Neutropaenia
Immune system disorders	
Uncommon	<i>Hypersensitivity</i>
Rare	<i>Angioedema, allergic reaction</i>
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, <i>aggression</i> , mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy
Rare	Disinhibition, suicidal behaviour, suicidal ideation
Not known	<i>Drug dependence</i>
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, <i>loss of consciousness</i> , psychomotor hyperactivity, dyskinesia, postural dizziness, intention tremor, nystagmus, cognitive disorder, <i>mental impairment</i> , speech disorder, hyporeflexia, hyperaesthesia, burning sensation, ageusia, <i>malaise</i>
Rare	<i>Convulsions</i> , parosmia, hypokinesia, dysgraphia, parkinsonism
Eye disorders	
Common	Blurred vision, 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	<i>Vision loss, keratitis</i> , 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, <i>congestive heart failure</i>
Rare	<i>QT prolongation</i> , 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	<i>Pulmonary oedema</i> , throat tightness
Not known	<i>Respiratory depression</i>

Gastrointestinal disorders	
Common	Vomiting, <i>nausea</i> , constipation, <i>diarrhoea</i> , flatulence, abdominal distension, dry mouth
Uncommon	Gastroesophageal reflux disease, salivary hypersecretion, oral hypoaesthesia
Rare	Ascites, pancreatitis, <i>swollen tongue</i> , dysphagia
Hepatobiliary disorders	
Uncommon	Elevated liver enzymes*
Rare	Jaundice
Very rare	Hepatic failure, hepatitis
Skin and subcutaneous tissue disorders	
Uncommon	Papular rash, urticaria, hyperhidrosis, <i>pruritus</i>
Rare	Toxic epidermal necrolysis, <i>Stevens Johnson syndrome</i> , 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, <i>urinary retention</i>
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Sexual dysfunction, delayed ejaculation, dysmenorrhoea, breast pain
Rare	Amenorrhoea, breast discharge, breast enlargement, <i>gynaecomastia</i>
General disorders and administration site conditions	
Common	Peripheral oedema, oedema, abnormal gait, fall, feeling drunk, feeling abnormal, fatigue
Uncommon	Generalised oedema, <i>face oedema</i> , 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 in some patients. The following reactions have been mentioned: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness. These symptoms may be 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 (see sections 4.2 and 4.4).

Paediatric population

The pregabalin safety profile observed in four 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

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via: ADR Reporting

Website: www.medicinesauthority.gov.mt/adrportal.

By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

Symptoms

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.

Management

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 antiepileptics; 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 ($\alpha 2\text{-}\delta$ 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 of up to 12 weeks, a reduction in both peripheral and central neuropathic pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials for 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 for 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 twice a day (BID) or three times a day (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.

A 12-week placebo-controlled study on patients with primary generalised tonic-clonic (PGTC) seizures included 219 subjects (5 to 65 years of age, of whom 66 between 5 and 16 years of age) who were assigned to pregabalin 5 mg/kg/day (maximum, 300 mg/day), 10 mg/kg/day (maximum, 600 mg/day) or placebo as adjunctive treatment. The percentage of subjects with at least a 50% reduction in PGTC seizure frequency 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 show 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. Ophthalmologic testing (including visual acuity testing, formal visual field testing and dilated funduscopy 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. Funduscopy 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.

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 $\geq 90\%$ 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 post-dose.

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 has been shown not to be 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

Capsule contents:

Pregelatinised maize starch

Talc (E553b)

Capsule shell:

Titanium dioxide (E171)

Gelatin

Yellow iron oxide (E172)

Black printing ink (shellac (E904), black iron oxide (E172), propylene glycol (E1520))

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Carton of blisters (PVC-PVDC/Al), containing 14, 28, 30, 56, 60, 84, 90, 98 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. PARALLEL IMPORT LICENSE HOLDER

NM Pharma Ltd.

3 / 4, Cantrija Complex, Triq it-Targa, il-Maghtab, Naxxar,
NXR6613
Malta

8. PARALLEL IMPORT LICENSE NUMBER

PI1438/05501A

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04th November 2021

10. DATE OF REVISION OF THE TEXT

February 2025