**SUMMARY OF PRODUCT CHARACTERISTICS**

# Lirapyn Capsules

(Pregabalin Capsules 25/50/75/150)

## 1. NAME OF THE MEDICINAL PRODUCT

Lirapyn Capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Lirapyn Capsules**

Each capsule contains
Pregabalin……...25 mg

**Lirapyn Capsules**
Each capsule contains
Pregabalin……...50 mg

**Lirapyn Capsules**
Each capsule contains
Pregabalin……75 mg

**Lirapyn Capsules**
Each capsule contains
Pregabalin……..150 mg
For full list of excipients, see **section 6.1**.

## 3. PHARMACEUTICAL FORM

Capsule

## 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.

## 4.2 Posology and method of administration

**Posology**
**Lirapyn Capsules** is available at the strengths of 25, 50 mg, 75 mg and 150 mg only and may not be suitable for all dosage recommendations mentioned below; other approved strengths or dosage forms should be considered in such cases.

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 below determined using the following formula:

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

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 below).

**Table: 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 pregabalin in children below the age of 12 years and in adolescents (12-17 years of age) have not been reported. Currently available data are described in **sections 4.8** and **5.2** but no recommendation on 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 may be taken with or without food.

Pregabalin is for oral use only.

## 4.3 Contraindications

Hypersensitivity to pregabalin or to any of the excipients of this product.

## 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 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 reported to be 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**
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. The incidence of visual acuity reduction and visual field changes was reported to be greater in pregabalin-treated patients than in placebo-treated patients; the incidence of fundoscopic changes was reported to be greater in placebo-treated patients.

Visual adverse reactions have also been reported during post marketing study 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 reported 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.

**Withdrawal symptoms**
After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been reported in some patients. The following events have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, nervousness, depression, pain, convulsion, hyperhidrosis and dizziness, suggestive of physical dependence. The patient should be informed about this at the start of the treatment.

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

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

**Congestive heart failure**
There have been reports of congestive heart failure in some patients receiving pregabalin. These reactions are mostly reported 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 reported to be 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 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**).

**Suicidal ideation and behaviour**
Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A small increased risk of suicidal ideation and behavior has been reported with anti-epileptic drugs. The mechanism of this risk is not known and the reported data do not exclude the possibility of an increased risk for pregabalin.

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

**Reduced lower gastrointestinal tract function**
There are 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 reported 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 reported at low doses of pregabalin (≤ 300 mg, aOR 1.52 [95% CI, 1.04 - 2.22]) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg, aOR 2.51 [95% CI 1.24 - 5.06]).

**Misuse, abuse potential or dependence**
Cases of misuse, abuse and dependence have been reported. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of 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.

**Excipients**
**Lirapyn Capsules** capsules contains mannitol which may have a mild laxative effect.

## 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.

**Reported *in vivo* studies and population pharmacokinetic analysis**
No clinically relevant pharmacokinetic interactions were reported between pregabalin and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. Oral antidiabetics, diuretics, insulin, phenobarbital, tiagabine and topiramate reportedly 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 medicinal products**
Pregabalin may potentiate the effects of ethanol and lorazepam.

In the reported 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. 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 reported in elderly volunteers. Interaction studies have only been reported in adults.

## 4.6 Pregnancy, lactation and fertility

**Women of childbearing potential / Contraception in males and females**
As the potential risk for humans is unknown, effective contraception must be used in women of child bearing potential.

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

Reproductive toxicity has been reported in animals (see **section 5.3**). The potential risk for humans is unknown.

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

**Lactation**
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 reported on the effects of pregabalin on female fertility.

No effects on sperm motility have been reported when healthy males were exposed to pregabalin at a dose of 600 mg/day for 3 months.

Adverse reproductive and developmental effects have been reported in male and female rats. 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 until it is known whether this medicinal product affects their ability to perform these activities.

## 4.8 Undesirable effects

The most commonly reported adverse reactions of pregabalin were dizziness and somnolence. Adverse reactions were usually mild to moderate in intensity. In reported studies, the discontinuation rate due to adverse reactions was 12% for patients receiving pregabalin and 5% for patients receiving placebo. The most commonly reported adverse reactions that led to discontinuation of pregabalin treatment include dizziness and somnolence.

In the table below all adverse reactions 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 reported to be increased.

Additional reactions reported from postmarketing experience are included in italics in the list below.

**Table: 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 |
| **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* |

| System Organ Class | Adverse drug reactions |
|---|---|
| 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).

After discontinuation of short-term and long-term treatment with pregabalin, withdrawal symptoms have been reported in some patients. The following reactions have been reported: insomnia, headache, nausea, anxiety, diarrhoea, flu syndrome, convulsions, nervousness, depression, pain, hyperhidrosis and dizziness, suggestive of

physical dependence. The patient should be informed about this at the start of the treatment.

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

***Paediatric population***
The pregabalin safety profile reported in paediatrics was similar to that reported in adults with epilepsy. The most common adverse events reported in the studies with pregabalin treatment were somnolence, pyrexia, upper respiratory tract infection, increased appetite, weight increased, and nasopharyngitis (see **sections 4.2** and **5.2**).

## 4.9 Overdose

The most commonly reported adverse reactions 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**).

# 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-epileptics, 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 ($\alpha_2$-$\delta$ protein) of voltage-gated calcium channels in the central nervous system.

## 5.2 Pharmacokinetics properties

Pregabalin steady-state pharmacokinetics are reported to be 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 reported 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***
Pregabalin has been reported to cross the blood brain barrier in mice, rats and monkeys. Pregabalin has also been reported 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. 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 reported to be directly proportional to creatinine clearance.

Dose adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see **section 4.2**).

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

***Gender***
It has been reported 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**).

***Hepatic impairment***
No specific pharmacokinetic studies were reported 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 reported 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 was reported 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 reported to be 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.

It has been reported 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 reported to be similar in paediatric and adult patients.

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

***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**).

***Breast-feeding mothers***

The pharmacokinetics of 150 mg pregabalin given every 12 hours (300 mg daily dose) was reported in 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 reported to be 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 reported to be well-tolerated at clinically relevant doses. In repeated dose toxicity studies in rats and monkeys CNS effects were reported, including hypoactivity, hyperactivity and ataxia. An increased incidence of retinal atrophy commonly reported in aged albino rats was reported after long-term exposure to pregabalin at exposures ≥5 times the mean human exposure at the maximum recommended clinical dose.

Pregabalin was not reported to be teratogenic in mice, rats or rabbits. Foetal toxicity in rats and rabbits was reported only at exposures sufficiently above human exposure. In reported 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 reported at exposures sufficiently in excess of therapeutic exposure. Adverse effects on male reproductive organs and sperm parameters were reported to be 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 reported results of a battery of *in vitro* and *in vivo* tests.

In two-year carcinogenicity studies with pregabalin in rats and mice, no tumours were reported 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 reported at exposures similar to the mean human exposure, but an increased incidence of haemangiosarcoma was reported 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 reported short-term and limited long-term clinical data. There is no reported evidence to suggest an associated risk to humans.

In juvenile rats the types of toxicity do not differ qualitatively from those reported in adult rats. However, juvenile rats are more sensitive. At therapeutic exposures, there was reported 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 reported at 5-fold the human therapeutic exposure. Reduced acoustic startle response was reported in juvenile rats 1-2 weeks after exposure at >2 times the human therapeutic exposure. Nine weeks after exposure, effect was no longer reported.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Mannitol, talc

### 6.2 Incompatibilities

Not Applicable

### 6.3 Shelf life

24 Months

### 6.4 Special precautions for storage

Store below 30ºC

### 6.5 Nature and contents of container

Lirapyn Capsules 75 mg are packed in Alu-PVC blister pack and each blister containing 7 Capsules.

Lirapyn Capsules 75 mg supplied in 4x7 pack size.

### 6.6 Special precautions for disposal and other handling

No special requirement.

## 7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceutical Industries Limited
Sun House, 201 B/1
Western Express Highway
Goregaon (East)
Mumbai -400 063
India

## 8. MARKETING AUTHORISATION NUMBER(S)

B4-8165

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

09/02/2018

## 10. DATE OF REVISION OF THE TEXT

March 2022

## REFERENCES

1. Summary of product characteristics of Lyrica Capsules, Upjohn UK Limited, November 2021.