SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM:

LYRICA® 25 mg Capsule

LYRICA® 50 mg Capsule

LYRICA® 75 mg Capsule

LYRICA® 100 mg Capsule

LYRICA® 150 mg Capsule

COMPOSITION:

Each hard capsule contains 25 mg, 50 mg, 75 mg, 100 mg or 150 mg of pregabalin.

Excipients: Lactose monohydrate, maize starch, talc.

PHARMACOLOGICAL CLASSIFICATION:

A 2.5 Central nervous system depressants – Anticonvulsants, including anti-epileptics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

The active substance, pregabalin, is a gamma-aminobutyric acid (GABA) analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid).

Mechanism of action:

In vitro studies show that pregabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin. Two lines of evidence indicate that binding of pregabalin to the α_2-δ site is required for analgesic activity in animal models: (1) Studies with the inactive R-enantiomer and other structural derivatives of pregabalin and (2) Studies of pregabalin in mutant mice with defective drug binding to the α_2-δ protein. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.

Pregabalin does not interact with either $GABA_A$ or $GABA_B$ receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of GABA uptake or degradation.

Pregabalin prevents pain-related behaviours in animal models of neuropathic and post-surgical pain, including hyperalgesia and allodynia.

Clinical experience:

Neuropathic pain:

The effectiveness of pregabalin for the management of neuropathic pain was investigated in 10 double-blind, placebo-controlled, multicentre studies with either twice a day (BD) or three times a day (TDS) dosing. A total of 2 099 patients were enrolled in the 10 studies. To enter the study, patients had to have moderate to severe pain caused by diabetic peripheral neuropathy or pain due to post-Herpes zoster infection.

Pharmacokinetic properties:

Pregabalin steady-state pharmacokinetics are similar in healthy volunteers and patients with chronic pain.

Absorption:

Pregabalin is absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration. Pregabalin oral bioavailability is estimated to be $\geq$ 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 pre-clinical studies, pregabalin has been shown to readily 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.

Metabolism:

Pregabalin undergoes negligible metabolism in humans. Following a dose of radio-labelled

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 pre-clinical 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 *Pharmacokinetics in special patient groups – Renal impairment*). Dosage adjustment in patients with reduced renal function or undergoing haemodialysis is necessary (see DOSAGE AND DIRECTIONS FOR USE, 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.

Pharmacokinetics in special patient groups:

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, dosage reduction in patients with renal impairment and dosage supplementation following haemodialysis is necessary (see DOSAGE AND DIRECTIONS FOR USE, 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.

Elderly (over 65 years of age):

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function (see DOSAGE AND DIRECTIONS FOR USE, Table 1).

INDICATIONS:

Neuropathic pain:

LYRICA is indicated for the treatment of adult patients with neuropathic pain due to Herpes zoster infections and diabetes.

CONTRAINDICATIONS:

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

WARNINGS AND SPECIAL PRECAUTIONS:

Effects on ability to drive and use machines:

LYRICA frequently causes dizziness and somnolence. Therefore, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medication affects their ability to perform these activities.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

There have been reports in the post-marketing experience of hypersensitivity reactions, including cases of angioedema and urticaria. LYRICA should be discontinued immediately if symptoms of angioedema, such as facial, perioral or upper airway swelling occur (see SIDE EFFECTS).

LYRICA treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall) in the elderly population. There have 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 medication (see SIDE EFFECTS).

When LYRICA is used in combination with antidepressants, respiratory failure has occurred.

After discontinuation of short-term and long-term treatment with LYRICA, withdrawal symptoms have been observed in some patients. The following events have been reported: insomnia, headache, nausea and diarrhoea (see SIDE EFFECTS).

Although the effects of discontinuation on the reversibility of renal failure have not been systematically studied, improved renal function following discontinuation or dose reduction of LYRICA has been reported (see SIDE EFFECTS). Renal failure has occurred.

There have been post-marketing reports of congestive heart failure or deterioration of heart failure in some patients receiving LYRICA. In short-term trials of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral oedema and cardiovascular complications such as hypertension or congestive heart failure. LYRICA should be used with caution in patients with congestive heart failure (see SIDE EFFECTS).

INTERACTIONS:

Since LYRICA 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, LYRICA is unlikely to produce, or be subject to, pharmacokinetic interactions.

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between LYRICA and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. In addition, population pharmacokinetic analysis indicated that the 3 commonly used drug classes, oral antidiabetics, diuretics and insulin, and the commonly used anti-epileptic drugs, phenytoin, carbamazepine, valproic acid, lamotrigine, phenobarbital, tiagabine, and topiramate, had no clinically significant effect on pregabalin clearance. Similarly, these analyses indicated that LYRICA had no clinically significant effect on the clearance of phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate and phenobarbital.

Co-administration of LYRICA with the oral contraceptives norethisterone and/or ethinyl oestradiol does

not influence the steady-state pharmacokinetics of either agent.

Multiple oral doses of LYRICA co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. LYRICA appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. LYRICA may potentiate the effects of ethanol and lorazepam.

In post-marketing experience, there are reports of respiratory failure and coma in patients taking LYRICA and other CNS depressant medications.

PREGNANCY AND LACTATION:

There are no adequate data on the use of LYRICA in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown. Therefore, LYRICA should not be used during pregnancy. It is not known if LYRICA is excreted in the breast milk of humans; however, it is present in the milk of rats. Therefore, breastfeeding is not recommended.

DOSAGE AND DIRECTIONS FOR USE:

LYRICA is given orally with or without food.

The recommended starting dose for LYRICA is 75 mg twice daily (150 mg/day), with or without food. Based on individual patient response and tolerability, the dose may be increased to 150 mg twice daily after an interval of 3 to 7 days.

In accordance with current clinical practice, if LYRICA has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Patients with renal impairment:

LYRICA is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. As LYRICA clearance is directly proportional to creatinine clearance (see *Pharmacokinetics in special patient groups – Renal impairment*), dosage 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:

$$CL_{cr}\ (ml/min) = \frac{(140 - age) \times Wt\ (kg)}{0{,}82 \times Serum\ creatinine\ (\mu mol/l)}$$

*For females multiply the CL_{cr} by 0,85

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

Creatinine clearance (CL_{cr}) (ml/min)	Total LYRICA daily dose*		Dose regimen
	Starting dose (mg/day)	Maximum dose (mg/day)	
≥ 60	150	300	BD
30 – 60	75	150	OD or BD
15 – 30	25 – 50	75	OD or BD
< 15	25	25 – 50	OD
Supplementary dosage following haemodialysis (mg)			
	25	50	Single dose+

BD = Two divided doses

OD = Once daily

*Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose

+Supplementary dose is a single additional dose

Use in patients with hepatic impairment:

No dosage adjustment is required for patients with hepatic impairment (see *Pharmacokinetics in special patient groups – Hepatic impairment*).

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

Use in the elderly (over 65 years of age):

No dosage adjustment is necessary for elderly patients unless their renal function is compromised, see Table 1.

SIDE EFFECTS:

The LYRICA clinical programme involved over 9 000 patients who were exposed to LYRICA, of whom over 5 000 were in double-blind placebo-controlled trials. The most commonly reported adverse reactions were dizziness and somnolence which were dose-related. Adverse reactions were usually mild to moderate in intensity. In all controlled studies, the discontinuation rate due to adverse events was 13 % for patients receiving LYRICA and 7 % for patients receiving placebo. The adverse reactions resulting in discontinuation from LYRICA 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, < 1/10), uncommon (> 1/1 000, <1/100) and rare (< 1/1 000).

The adverse reactions listed may also be associated with the underlying disease and concomitant medications.

Body system	**Adverse drug reactions**
Blood and lymphatic system disorders	
Rare	Neutropenia
Metabolism and nutrition disorders	
Common	Appetite increased
Uncommon	Anorexia
Rare	Hypoglycaemia
Psychiatric disorders	
Common	Euphoric mood, confusion, libido decreased, irritability
Uncommon	Depersonalisation, anorgasmia, restlessness, depression, agitation, mood swings, insomnia exacerbated, depressed mood, word finding difficulty, hallucination, abnormal dreams, libido increased, panic attack, apathy
Rare	Disinhibition, elevated mood
Nervous system disorders	
Very common	Dizziness, somnolence

Common	Ataxia, disturbance in attention, coordination abnormal, memory impairment, tremor, dysarthria, paraesthesia
Uncommon	Cognitive disorder, hypoaesthesia, visual field defect, nystagmus, speech disorder, myoclonus, hyporeflexia, dyskinesia, psychomotor hyperactivity, dizziness postural, hyperaesthesia, ageusia, burning sensation, intention tremor, stupor, syncope
Rare	Hypokinesia, parosmia, dysgraphia
Eye disorders	
Common	Vision blurred, diplopia
Uncommon	Visual disturbance, dry eye, eye swelling, visual acuity reduced, eye pain, asthenopia, lacrimation increased
Rare	Photopsia, eye irritation, mydriasis, oscillopsia, altered visual depth perception, peripheral vision loss, strabismus, visual brightness
Ear and labyrinth disorders	
Common	Vertigo
Rare	Hyperacusis
Cardiac disorders	
Uncommon	Tachycardia
Rare	Atrioventricular block first degree, sinus tachycardia, sinus arrhythmia, sinus bradycardia
Vascular disorders	
Uncommon	Flushing, hot flushes
Rare	Hypotension, peripheral coldness, hypertension
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea, nasal dryness
Rare	Nasopharyngitis, cough, nasal congestion, epistaxis, rhinitis, snoring, throat tightness
Gastrointestinal disorders	

Common	Dry mouth, constipation, vomiting, flatulence
Uncommon	Abdominal distension, salivary hypersecretion, gastroesophageal reflux disease, hypoaesthesia oral
Rare	Ascites, dysphagia, pancreatitis
Skin and subcutaneous tissue disorders	
Uncommon	Sweating, rash papular
Rare	Cold sweat, urticaria
Musculoskeletal and connective tissue disorders	
Uncommon	Muscle twitching, joint swelling, muscle cramp, myalgia, arthralgia, back pain, pain in limb, muscle stiffness
Rare	Cervical spasm, neck pain, rhabdomyolysis
Renal and urinary disorders	
Uncommon	Dysuria, urinary incontinence
Rare	Oliguria, renal failure
Reproductive system and breast disorders	
Common	Erectile dysfunction
Uncommon	Ejaculation delayed, sexual dysfunction
Rare	Amenorrhoea, breast pain, breast discharge, dysmenorrhoea, hypertrophy breast
General disorders and administration site conditions	
Common	Fatigue, oedema peripheral, feeling drunk, oedema, gait abnormal
Uncommon	Asthenia, fall, thirst, chest tightness
Rare	Pain exacerbated, anasarca, pyrexia, rigors
Investigations	
Common	Weight increased
Uncommon	Alanine aminotransferase increased, blood creatine phosphokinase increased, aspartate aminotransferase increased, platelet count decreased

Rare	Blood glucose increased, blood creatinine increased, blood potassium decreased, weight decreased, white blood cell count decreased

Elderly (over 65 years of age):

In a total of 998 elderly patients, no overall differences in safety were observed compared with patients less than 65 years of age.

Post-marketing: (see WARNINGS AND SPECIAL PRECAUTIONS)

Immune system disorder:

Angioedema, allergic reaction, hypersensitivity.

Gastrointestinal disorders:

Rare cases of swollen tongue have been reported, diarrhoea, nausea.

Cardiac disorders:

Congestive heart failure.

Skin and subcutaneous tissue disorders:

Rare cases of face swelling have been reported, pruritus.

Nervous system disorders:

Headache, loss of consciousness, mental impairment, reversible paralysis.

Renal and urinary disorders:

Urinary retention.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In overdoses up to 15 g, no unexpected adverse reactions were reported.

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

Treatment of LYRICA overdose should include general supportive measures and may include haemodialysis if necessary (see DOSAGE AND DIRECTIONS FOR USE – Patients with renal impairment).

IDENTIFICATION:

LYRICA 25 mg: White, opaque, hard gelatine capsule, marked “Pfizer” on the cap and “PGN 25” on the body with black ink.

LYRICA 50 mg: White, opaque, hard gelatine capsule, marked “Pfizer” on the cap and “PGN 50” on the body with black ink. The body is also marked with a black band.

LYRICA 75 mg: White (body) and orange (cap), opaque, hard gelatine capsule, marked “Pfizer” on the cap and “PGN 75” on the body with black ink.

LYRICA 100 mg: Orange, opaque, hard gelatine capsule, marked “Pfizer” on the cap and “PGN 100” on the body with black ink.

LYRICA 150 mg: White, opaque, hard gelatine capsule, marked “Pfizer” on the cap and “PGN 150” on the body with black ink.

PRESENTATION:

Clear PVC/Aluminium blisters containing 14, 56 or 100 hard capsules.

STORAGE INSTRUCTIONS:

Store at room temperature, below 25 °C.

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

LYRICA 25 mg: A39/2.5/0264

LYRICA 50 mg: A39/2.5/0265

LYRICA 75 mg: A39/2.5/0266

LYRICA 100 mg: A39/2.5/0267

LYRICA 150 mg: A39/2.5/0268

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Upjohn South Africa (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT:

02 February 2010

BOTSWANA: S2

LYRICA 25 mg – Reg. No: BOT1101872

LYRICA 75 mg – Reg. No: BOT1101874

LYRICA 150 mg – Reg. No: BOT1101876

NAMIBIA: NS3

LYRICA 25 mg – Reg. No: 08/2.5/0150

LYRICA 75 mg – Reg. No: 08/2.5/0152

LYRICA 150 mg – Reg. No: 08/2.5/0154

ZIMBABWE: PP10

LYRICA 25 mg – Reg. No: 2016/13.1/5304

LYRICA 75 mg – Reg. No: 2016/13.1/5305

LYRICA 150 mg – Reg. No: 2016/13.1/5306