CONFIDENTIAL

PYLIXA

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

PYLIXA 25, 25 mg hard capsules

PYLIXA 50, 50 mg hard capsules

PYLIXA 75, 75 mg hard capsules

PYLIXA 100, 100 mg hard capsules

PYLIXA 150, 150 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sugar (mannitol).

PYLIXA strength:	Mannitol content
25 mg	10,60 mg
50 mg	21,20 mg
75 mg	31,80 mg
100 mg	42,40 mg
150 mg	63,60 mg

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules, hard

PYLIXA 25 hard capsules are presented as white powder in a white cap and white body hard gelatin capsule, imprinted with "25" on the body.

PYLIXA 50 hard capsules are presented as white powder in a white cap and white body hard gelatin capsule, imprinted with "50" on the body.

PYLIXA 75 hard capsules are presented as white powder in a Swedish orange cap and white body hard gelatin capsule, imprinted with "75" on the body.

PYLIXA 100 hard capsules are presented as white powder in a Swedish orange cap and Swedish orange body hard gelatin capsule, imprinted with "100" on the body.

PYLIXA 150 hard capsules are presented as white powder in a white cap and white body hard gelatin capsule, imprinted with "150" on the body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PYLIXA capsules are indicated for the treatment of adult patients with neuropathic pain due to Herpes zoster infections and diabetes.

4.2 Posology and method of administration

Posology:

The recommended starting dose for **PYLIXA** 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 **PYLIXA** has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

Special Populations

Patients with renal impairment:

PYLIXA is eliminated from the systemic circulation primarily by renal excretion as unchanged pregabalin. As **PYLIXA** clearance is directly proportional to creatinine clearance (see section 5.2), dosage reduction in patients with compromised renal function must be individualised according to creatinine clearance (CLcr), as indicated in Table 1 determined using the following formula:

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

Table 1: PYLIXA dosage adjustment based on renal function			
Creatinine clearance (CL_{CR}) (ml/min)	**Total PYLIXA 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

PYLIXA is removed effectively from plasma by haemodialysis (50 % of medicine in 4 hours). For patients receiving haemodialysis, the **PYLIXA** 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).

Use in patients with hepatic impairment:

No dosage adjustment is required for patients with hepatic impairment (see section 5.2).

Paediatric patients:

The safety and effectiveness of **PYLIXA** 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.

Method of administration

PYLIXA is given orally with or without food.

4.3 Contraindications

Known hypersensitivity to pregabalin or to any of the excipients of **PYLIXA** (see section 6.1).

4.4 Special warnings and precautions for use

Diabetic patients

Diabetic patients who gain weight on **PYLIXA** treatment may need to adjust hypoglycaemic medicines.

Hypersensitivity reactions

PYLIXA 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

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

reports of loss of consciousness, confusion and mental impairment. Patients should be advised to exercise caution until they are familiar with the potential effects of **PYLIXA.**

Vision-related effects

Visual adverse reactions have been reported, including loss of vision, visual blurring or other changes of visual acuity, many of which were transient. Discontinuation of **PYLIXA** may result in resolution or improvement of these visual symptoms.

Renal failure

Renal failure has been reported and discontinuation of pregabalin, as in **PYLIXA**, did show reversibility of this adverse reaction.

Withdrawal symptoms

After discontinuation of short-term and long-term treatment with pregabalin, as in **PYLIXA**, withdrawal symptoms have been observed. The following events have been mentioned: 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 **PYLIXA** use or shortly after discontinuing.

Discontinuation of long-term treatment of pregabalin, as in **PYLIXA**, data suggest that the incidence and severity of withdrawal symptoms may be dose related.

Congestive heart failure

Congestive heart failure has been reported. These reactions are mostly seen in elderly cardiovascular compromised patients during pregabalin treatment for a neuropathic indication. **PYLIXA** should be used with caution in these patients. Discontinuation of **PYLIXA** may resolve the reaction.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with gabapentinoids such as pregabalin in **PYLIXA** in several indications. Therefore, patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients and caregivers should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Reduced lower gastrointestinal tract function

Reduced lower gastrointestinal tract function (e.g. intestinal obstruction, paralytic ileus, constipation) has been reported when pregabalin was co-administered with medicines that have the potential to produce constipation, such as opioid analgesics. When **PYLIXA** and opioids will be used in combination, measures to prevent constipation may be considered (especially in female patients and the elderly).

Concomitant use with opioids

Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression (see section 4.5). In a case control study of opioid users, those patients who took pregabalin concomitantly with an opioid had an increased risk for opioid-related death compared to opioid use alone. This increased risk was observed at low doses of

pregabalin (≤ 300 mg) and there was a trend for a greater risk at high doses of pregabalin (> 300 mg).

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 **PYLIXA** misuse, abuse or dependence (development of tolerance, dose escalation, intentional overdose, drug-seeking behaviour have been reported).

Encephalopathy

Encephalopathy has been reported, mostly in patients with underlying conditions that may precipitate encephalopathy.

4.5 Interaction with other medicines 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 medicine metabolism *in vitro*, and is not bound to plasma proteins, **PYLIXA** is unlikely to produce, or be subject to, pharmacokinetic interactions.

***In vivo* studies and population pharmacokinetic analysis**

Accordingly, in *in vivo* studies no clinically relevant pharmacokinetic interactions were observed between **PYLIXA** and phenytoin, carbamazepine, valproic acid, lamotrigine, gabapentin, lorazepam, oxycodone or ethanol. In addition, population pharmacokinetic analysis indicated that the 3 commonly used medicine classes, oral antidiabetics, diuretics and insulin, and the commonly used anti-epileptic medicines, phenytoin, carbamazepine,

valproic acid, lamotrigine, phenobarbitone, tiagabine and topiramate had no clinically significant effect on pregabalin clearance.

Similarly, these analyses indicated that **PYLIXA** had no clinically significant effect on the clearance of phenytoin, carbamazepine, valproic acid, lamotrigine, topiramate and phenobarbitone.

Oral contraceptives, norethisterone and/or ethinyl oestradiol

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

Central nervous system influencing medicines

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

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

Interactions and the elderly

No specific pharmacodynamic interaction studies were conducted in elderly volunteers. Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/ contraception in males and females

As potential risk for humans is unknown, effective contraception must be used in women of child-bearing potential.

Pregnancy

There are no adequate data on the use of **PYLIXA** in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk to humans is unknown. Therefore, **PYLIXA** should not be used during pregnancy.

Breast-feeding

Pregabalin is excreted into human milk (see section 5.2). The effect of pregabalin on new-borns/infants is unknown. Therefore, breastfeeding is not recommended during treatment with **PYLIXA**.

Fertility

There are no clinical data on the effects of pregabalin on female fertility. A fertility study in female rats has shown adverse reproductive effects. Fertility studies in male rats have shown adverse reproductive and development effects.

4.7 Effects on ability to drive and use machines

PYLIXA frequently causes dizziness and somnolence. Head and body injuries and road traffic incidents have also been reported with pregabalin, as contained in **PYLIXA**. Therefore, patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicine affects their ability to perform these activities.

4.8 Undesirable effects

a) Summary of adverse effects

The most frequently reported adverse reactions were dizziness and somnolence. The most frequent adverse reactions resulting in discontinuation from pregabalin treatment are dizziness and somnolence.

In the table below the adverse reactions are listed by system organ class and frequency. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Additional reactions reported from post marketing experience are also included and listed according to frequency.

b) Tabulated summary of adverse reactions

MedDRA system organ class	**Frequency**	**Adverse reactions**
Infections and infestations:	Frequent	Nasopharyngitis
Blood and the lymphatic system disorders	Less frequent	Neutropenia
Immune system disorders	Less frequent	Hypersensitivity, angioedema, allergic reaction
Metabolism and	Frequent	Increased appetite

MedDRA system organ class	**Frequency**	**Adverse reactions**
nutrition disorders		
	Less frequent	Anorexia, hypoglycaemia
Psychiatric disorders	Frequent	Euphoric mood, confusion, irritability, disorientation, insomnia, decreased libido
	Less frequent	Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, increased libido, anorgasmia, apathy, disinhibition
	Unknown frequency	Suicidal ideation and behaviour
Nervous system disorders	Frequent	Dizziness, somnolence, headache, ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		paraesthesia, hypoaesthesia, sedation, balance disorder, lethargy
	Less frequent	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, convulsions, parosmia, hypokinesia, dysgraphia
Eye disorders	Frequent	Blurred vision, diplopia
	Less frequent	Peripheral vision loss, visual disturbance, eye swelling, visual field defect, reduced visual acuity, eye pain, asthenopia, photopsia, dry eye, increased lacrimation, eye irritation, vision loss, keratitis, oscillopsia, altered visual depth perception,

MedDRA system organ class	**Frequency**	**Adverse reactions**
		mydriasis, strabismus, visual brightness
Ear and labyrinth disorders	Frequent	Vertigo
	Less frequent	Hyperacusis
Cardiac disorders	Less frequent	Tachycardia, first degree atrioventricular block, sinus bradycardia, congestive heart failure, QT prolongation, sinus tachycardia, sinus dysrhythmia
Vascular disorders	Less frequent	Hypotension, hypertension, hot flushes, flushing, peripheral coldness
Respiratory, thoracic and mediastinal disorders:	Less frequent	Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness, pulmonary oedema, throat tightness
Gastrointestinal disorders:	Frequent	Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal distension, dry mouth

MedDRA system organ class	**Frequency**	**Adverse reactions**
	Less frequent	Gastro-oesophageal reflux disease, salivary hypersecretion, oral hypoaesthesia, ascites, pancreatitis, swollen tongue, dysphagia
Hepatobiliary disorders	Less frequent	Elevated liver enzymes*, jaundice, hepatic failure, hepatitis
Skin and subcutaneous tissue disorders:	Less frequent	Papular rash, urticaria, hyperhidrosis, pruritus, Stevens- Johnson syndrome, cold sweat
Musculoskeletal and connective tissue disorders:	Frequent	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm
	Less frequent	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness, rhabdomyolysis
Renal and urinary disorders:	Less frequent	Urinary incontinence, dysuria, renal failure, oliguria, urinary retention
	Frequent	Erectile dysfunction

MedDRA system organ class	**Frequency**	**Adverse reactions**
Reproductive system and breast disorders	Less frequent	Sexual dysfunction, delayed ejaculation, dysmenorrhoea, breast pain, amenorrhoea, breast discharge, breast enlargement, gynaecomastia
General disorders and administration site conditions:	Frequent	Peripheral oedema, oedema, abnormal gait, fall, feeling drunk, feeling abnormal, fatigue
	Less frequent	Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia
Investigations:	Frequent	Increased weight
	Less frequent	Increased blood creatine phosphokinase, increased alanine aminotransferase, increased aspartate aminotransferase, increased blood glucose, decreased platelet count, increased blood creatinine, decreased blood potassium, decreased weight, decreased white blood cell count

* Alanine aminotransferase increased (ALT) and aspartate aminotransferase increased (AST).

c) Description of selected adverse reactions

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, 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In the post marketing experience, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included affective disorder, somnolence, confusional state, agitation, depression and restlessness. Seizures were also reported. In rare occasions, cases of coma have been reported.

Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 2.5 Central nervous sytem depressants – Anticonvulsants: including antiepileptics.

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

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

Pregabalin binds to an auxiliary subunit (α_2-σ protein) of voltage-gated calcium channels in the central nervous system, displacing (3H)-gabapentin.

Two lines of evidence indicate that binding of pregabalin to the α_2-σ 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 binding to the α_2-σ 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 GABAA or GABAB 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.

5.2 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 ≥ 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 unchanged from the systemic circulation primarily by renal excretion.

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 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 single-dose data.

Special Populations:

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 section 4.2).

Elderly (over 65 years of age):

Pregabalin clearance tends to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with decreases in creatinine clearance associated with increasing age. Reduction of pregabalin dose may be required in patients who have age related compromised renal function (see section 4.2).

Gender:

Clinical trials indicate that gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hard capsules content:

Pregelatinised maize starch

Mannitol

Talc

Hard capsule shell content:

Gelatin

Titanium dioxide (E171)

Red iron oxide (E172) *(only in capsules shells of PYLIXA 75 and 100 capsules).*

Black printing ink, containing

Shellac

Black iron oxide (E172)

Propylene glycol (E1520)

Ammonium hydroxide (E527)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 ˚C. Keep blisters in carton until required for use.

Keep the container well closed.

6.5 Nature and contents of container

Cartons of 14, 56, 60 or 100 hard capsules, packed in clear PVC/Aluminium foil blisters.

Bottles with 60 or 100 hard capsules, packed in white opaque HDPE bottles with a white PP screw cap with an induction seal liner.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Spear Pharmaceuticals (Pty) Ltd

2 Bruton Road

Block C, Nicol Main Office Park

Bryanston

2191

South Africa

8. REGISTRATION NUMBERS

PYLIXA 25: 51/2.5/0900

PYLIXA 50: 51/2.5/0901

PYLIXA 75: 51/2.5/0902

PYLIXA 100: 51/2.5/0903

PYLIXA 150: 51/2.5/0904

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07 September 2021

10. DATE OF REVISION OF THE TEXT

23 February 2022