

**Approved Professional Information for Medicines for Human Use: PRERICA**

**SCHEDULING STATUS**

**S5**

**1. NAME OF THE MEDICINE**

PRERICA 25 mg hard capsules

PRERICA 50 mg hard capsules

PRERICA 75 mg hard capsules

PRERICA 100 mg hard capsules

PRERICA 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 mannitol

PRERICA 25 mg: 15 mg mannitol per capsule

PRERICA 50 mg: 30 mg mannitol per capsule

PRERICA 75 mg: 7,5 mg mannitol per capsule

PRERICA 100 mg: 10 mg mannitol per capsule

PRERICA 150 mg: 20 mg mannitol per capsule

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Capsules, hard

PRERICA 25 mg hard capsules

White cap and white body, hard gelatine capsules size 4, containing a white or almost white powder or cylindrical mass that disintegrates when touched. Markings on body: "PGB 25" in black ink.

#### PRERICA 50 mg hard capsules

White cap and white body, hard gelatine capsules size 3, containing a white or almost white powder or cylindrical mass that disintegrates when touched. Markings on body: "PGB 50" in black ink with a black band.

#### PRERICA 75 mg hard capsules

Orange cap and white body, hard gelatine capsules size 4, containing a white or almost white powder or cylindrical mass that disintegrates when touched. Markings on body: "PGB 75" in black ink.

#### PRERICA 100 mg hard capsules

Orange cap and orange body, hard gelatine capsules size 3, containing a white or almost white powder or cylindrical mass that disintegrates when touched. Markings on body: "PGB 100" in black ink.

#### PRERICA 150 mg hard capsules

White cap and white body, hard gelatine capsules size 2, containing a white or almost white powder or cylindrical mass that disintegrates when touched. Markings on body: "PGB 150" in black ink.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

#### *Neuropathic pain*

PRERICA is 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 PRERICA 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 PRERICA must be discontinued, it is recommended this should be done gradually over a minimum of 1 week.

## Special populations

### *Use in patients with renal impairment*

PRERICA is eliminated from the systemic circulation primarily by renal excretion as unchanged pregabalin.

As PRERICA clearance is directly proportional to creatinine clearance (see section 5.2 – 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:

$$CL_{CR(mL/min)} = \left[ 1,23 \times \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/L)}} \right] (\times 0,85 \text{ for female patients})$$

**Table 1. PRERICA dosage adjustment based on renal function**

Creatinine clearance ( $CL_{CR}$ ) (mL/min)	Total PRERICA 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 <sup>+</sup>
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BD = Two divided doses; OD = Once daily

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

<sup>+</sup>Supplementary dose is a single additional dose

PRERICA is removed effectively from plasma by haemodialysis (50 % of the active ingredient in 4 hours). For patients receiving haemodialysis, the PRERICA 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 PRERICA in patients below the age of 18 years with neuropathic pain has not been established.

#### ***Use in the elderly population (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**

PRERICA is given orally with or without food.

#### **4.3 Contraindications**

Hypersensitivity to pregabalin or to any of the excipients of PRERICA (see section 6.1).

#### **4.4 Special warnings and precautions for use**

##### ***Diabetic patients***

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

##### ***Hypersensitivity reactions***

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***

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

##### ***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 PRERICA may result in resolution or improvement of these visual symptoms.

##### ***Renal failure***

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

##### ***Withdrawal symptoms***

After discontinuation of short-term and long-term treatment with pregabalin, as in PRERICA, 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 PRERICA use or shortly after discontinuing.

Discontinuation of long-term treatment of pregabalin, as in PRERICA, 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. PRERICA should be used with caution in these patients. Discontinuation of PRERICA may resolve the reaction.

### ***Suicidal ideation and behaviour***

Suicidal ideation and behaviour have been reported in patients treated with gabapentinoids such as pregabalin in PRERICA 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 PRERICA 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 reported case-control studies of opioid users, 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 ( $\leq 300$  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 PRERICA 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, PRERICA 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 PRERICA 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 PRERICA 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 PRERICA 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 PRERICA co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. PRERICA appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. PRERICA may potentiate the effects of ethanol and lorazepam.

In the post marketing experience, there are reports of respiratory failure and coma in patients taking PRERICA 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 childbearing potential / Contraception in males and females**

As the potential risk for humans is unknown, effective contraception must be used in women of childbearing potential.

##### **Pregnancy**

There are no adequate data from the use of PRERICA in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

Therefore, PRERICA should not be used during pregnancy.

##### **Breastfeeding**

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

##### **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 developmental effects.

#### **4.7 Effects on ability to drive and use machines**

PRERICA frequently causes dizziness and somnolence. Head and body injuries and road traffic incidents have also been reported with pregabalin, as contained in PRERICA. 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

<b>MedDRA System Organ Class</b>	<b>Frequent</b>	<b>Less Frequent</b>	<b>Unknown frequency</b>
<b>Infections and infestations</b>	Nasopharyngitis		
<b>Blood and lymphatic system disorders</b>		Neutropoenia	
<b>Immune system disorders</b>		Hypersensitivity, angioedema, allergic reaction	
<b>Metabolism and nutrition disorders</b>	Increased appetite	Anorexia, hypoglycaemia	

<p><b>Psychiatric disorders</b></p>	<p>Euphoric mood, confusion, irritability, disorientation, insomnia, decreased libido</p>	<p>Hallucination, panic attack, restlessness, agitation, depression, depressed mood, elevated mood, aggression, mood swings, depersonalisation, word finding difficulty, abnormal dreams, libido increased, anorgasmia, apathy, disinhibition</p>	<p>Suicidal ideation and behaviour</p>
<p><b>Nervous system disorders</b></p>	<p>Dizziness, somnolence, headache, ataxia, coordination abnormal, tremor, dysarthria, amnesia, memory impairment, disturbance in attention, paraesthesia, hypoaesthesia,</p>	<p>Syncope, stupor, myoclonus, loss of consciousness, psychomotor hyperactivity, dyskinesia, dizziness postural, intention tremor, nystagmus, cognitive disorder, mental impairment, speech disorder,</p>	

	sedation, balance disorder, lethargy	hyporeflexia, hyperaesthesia, burning sensation, ageusia, malaise, convulsions, parosmia, hypokinesia, dysgraphia	
<b>Eye disorders</b>	Blurred vision, diplopia	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, mydriasis, strabismus, visual brightness	
<b>Ear and labyrinth disorders</b>	Vertigo	Hyperacusis	

<b>Cardiac disorders</b>		Tachycardia, first degree atrioventricular block, sinus bradycardia, congestive heart failure, QT prolongation, sinus tachycardia, sinus dysrhythmia	
<b>Vascular disorders</b>		Hypotension, hypertension, hot flushes, flushing, peripheral coldness	
<b>Respiratory, thoracic and mediastinal disorders</b>		Dyspnoea, epistaxis, cough, nasal congestion, rhinitis, snoring, nasal dryness, pulmonary oedema, throat tightness	
<b>Gastrointestinal disorders</b>	Vomiting, nausea, constipation, diarrhoea, flatulence, abdominal	Gastroesophageal reflux disease, salivary hypersecretion, oral hypoaesthesia, ascites, pancreatitis,	

	distension, dry mouth	swollen tongue, dysphagia	
<b>Hepatobiliary disorders</b>		Elevated liver enzymes*, jaundice, hepatic failure, hepatitis	
<b>Skin and subcutaneous tissue disorders</b>		Papular rash, urticaria, hyperhidrosis, pruritus, Stevens Johnson syndrome, cold sweat	
<b>Musculoskeletal and connective tissue disorders</b>	Muscle cramp, arthralgia, back pain, pain in limb, cervical spasm	Joint swelling, myalgia, muscle twitching, neck pain, muscle stiffness, rhabdomyolysis	
<b>Renal and urinary disorders</b>		Urinary incontinence, dysuria, renal failure, oliguria, urinary retention	
<b>Reproductive system and breast disorders</b>	Erectile dysfunction	Sexual dysfunction, delayed ejaculation, dysmenorrhoea, breast pain, amenorrhoea,	

		breast discharge, breast enlargement, gynaecomastia	
<b>General disorders and administration site conditions</b>	Peripheral oedema, oedema, abnormal gait, fall, feeling drunk, feeling abnormal, fatigue	Generalised oedema, face oedema, chest tightness, pain, pyrexia, thirst, chills, asthenia	
<b>Investigations</b>	Increased weight increased	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 reported 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, reported 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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “**6.04 Adverse Drug Reaction Reporting Form**”, found online under SAHPRA’s publications:

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

### **4.9 Overdose**

In documented post marketing experiences, the most commonly reported adverse reactions observed when pregabalin was taken in overdose included somnolence, confusional state, agitation, and restlessness. Seizures were also reported.

In rare occasions, cases of coma have been reported.

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

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Category and Class: A 2.5 Central nervous system 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 ( $\alpha 2\text{-}\delta$  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  $\alpha 2\text{-}\sigma$  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  $\alpha 2\text{-}\sigma$  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<sub>A</sub> or GABA<sub>B</sub> 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  $\geq 90\%$  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 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 section 5.2 “Pharmacokinetics in special patient groups – 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.

### **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, dose reduction in patients with renal impairment and dose supplementation following haemodialysis is necessary (see section 4.2 Table 1).

#### ***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 Table 1).

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### *Capsule fill content*

Mannitol

Co-processed compendial corn starch and compendial pregelatinized corn starch

Talc

#### *Hard Capsule Body*

Gelatine

Iron Oxide Red (E172)

Titanium dioxide (E171)

#### *Hard Capsule Cap*

Gelatin

Iron Oxide Red (E172)

Titanium dioxide (E171)

#### *Printing ink (Black)*

Black Iron Oxide (E172)

Potassium hydroxide

Shellac

### **6.2 Incompatibilities**

Not applicable

### **6.3 Shelf life**

24 months

#### **6.4 Special precautions for storage**

Store at or below 25 °C.

#### **6.5 Nature and contents of container**

The product will be packed in Aluminium/PVC blisters or HDPE containers with PP screw cap.

Blisters 30's, 56's, 60's, 84's, 90's. Bulk 100's.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal**

No special requirements

### **7. HOLDER OF CERTIFICATE OF REGISTRATION**

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

### **8. REGISTRATION NUMBER(S)**

PRERICA 25 mg capsules: 50/2.5/0715

PRERICA 50 mg capsules: 50/2.5/0716

PRERICA 75 mg capsules: 50/2.5/0717

Austell Pharmaceuticals (Pty) Ltd, 50/2.5/0715-9, PRERICA 25 mg, 50 mg, 75 mg, 100 mg and 150 mg hard-gelatin capsules

PRERICA 100 mg capsules: 50/2.5/0718

PRERICA 150 mg capsules: 50/2.5/0719

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

07 December 2021

## **10. DATE OF REVISION OF THE TEXT**

30 November 2022