**PROFESSIONAL INFORMATION FOR PRIMEMAK 15 MG AND 30 MG EXTENDED RELEASE CAPSULES**

**SCHEDULING STATUS:** **S5**

## 1. NAME OF THE MEDICINE

**PRIBEMAK 15** (extended release capsule)

**PRIBEMAK 30** (extended release capsule)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**PRIBEMAK 15**: Each extended release capsule contains 15 mg cyclobenzaprine (as hydrochloride).

**PRIBEMAK 30**: Each extended release capsule contains 30 mg cyclobenzaprine (as hydrochloride).

**PRIBEMAK 15**: contains 49,8 mg sugar (sucrose).

**PRIBEMAK 30**: contains 99,60 mg sugar (sucrose).

For the full list of excipients, see **section 6.1**

## 3. PHARMACEUTICAL FORM

Capsules

**PRIBEMAK 15:** Size ‘4’ capsule, containing white to off white pellets, having orange cap, orange body with ‘T39’ imprinted on the cap and ’15 mg’ imprinted on the body with black ink.

**PRIBEMAK 30:** Size ‘4’ capsule, containing white to off white pellets, having orange cap, blue body with ‘T40’ imprinted on the cap and ’30 mg’ imprinted on the body with white ink.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**PRIBEMAK** is indicated as an adjunct to rest and physiotherapy for relief of muscle spasm associated

with acute, painful, musculoskeletal conditions.

**PRIBEMAK** should be used for short period (up to two to three weeks) because adequate evidence of effectiveness for more prolonged use is not available and because muscle spasm associated with acute, painful, musculoskeletal conditions is generally of short duration and specific therapy for longer periods is seldom warranted.

**PRIBEMAK** has been found to be not effective in the treatment of spasticity associated with cerebral or spinal cord disease or in children with cerebral palsy.

**4.2 Posology and method of administration**

**Posology**

The recommended adult dose is 15 mg once daily.

Some patients may require up to 30 mg/day given as one 30 mg capsule once daily or 2 x 15 mg capsules taken once daily.

Doses must be taken at approximately the same time each day. Use of **PRIBEMAK** for periods longer than two or three weeks is not recommended. (See **section 4.1**)

**Special populations**

*Elderly:*

**PRIBEMAK** should not be used in the elderly. (see **section 4.3**).

*Hepatic impairment:*

**PRIBEMAK** should not be used in patients with hepatic impairment. (See **section 4.3**).

*Paediatric population*

Safety and effectiveness of **PRIBEMAK** has not been established in paediatric patients.

**Method of administration**

For oral use.

**4.3 Contraindications**

**PRIBEMAK** is contraindicated:

- In patients with a history of hypersensitivity to the active substance or to any of the excipients listed in **section 6.1**.
- Concomitant use of monoamine oxidase (MAO) inhibitors or within 14 days after their discontinuation. Hyperpyretic crisis, seizures and deaths have occurred in patients receiving cyclobenzaprine (or structurally similar tricyclic antidepressants) concomitantly with MAO inhibitor medicines.
- During the acute recovery phase of myocardial infarction, and in patients with dysrhythmias, heart block or conduction disturbances, or congestive heart failure.
- Hyperthyroidism.
- Use of **PRIBEMAK** is not recommended in patients with mild, moderate or severe hepatic impairment. This is as a result of a two-fold higher cyclobenzaprine plasma level in subjects with mild hepatic impairment, as compared to healthy subjects, following immediate release cyclobenzaprine and because there is limited dosing flexibility with **PRIBEMAK**.
- Use of **PRIBEMAK** is not recommended in the elderly. This is due to a 40 % increase in cyclobenzaprine plasma levels and a 56 % increase in plasma half-life following administration of **PRIBEMAK** in elderly subjects as compared to young adults.

**4.4 Special warnings and precautions for use**

**Serotonin syndrome**

The development of a potentially life-threatening serotonin syndrome has been reported with cyclobenzaprine when used in combination with other medicines, such as selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tramadol, bupropion, meperidine, verapamil, or MAO inhibitors. The concomitant use of **PRIBEMAK** with MAO inhibitors is contraindicated (see **section 4.3**). Serotonin syndrome symptoms may include mental status changes (e.g., confusion, agitation, hallucinations), autonomic instability (e.g. diaphoresis, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. tremor, ataxia, hyperreflexia, clonus, muscle rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea). Treatment with **PRIBEMAK** and any

concomitant serotonergic medicines should be discontinued immediately. If the above reactions occur and supportive symptomatic treatment should be initiated. If concomitant treatment with **PRIBEMAK** and other serotonergic medicines is clinically warranted, careful observation is advised, particularly during treatment initiation or dose increases.

**Tricyclic antidepressant-like effects**

Cyclobenzaprine is structurally related to the tricyclic antidepressants, e.g. amitriptyline and imipramine. Tricyclic antidepressants have been reported to produce dysrhythmias, sinus tachycardia, prolongation of the conduction time leading to myocardial infarction and stroke (see **section 4.3**). **PRIBEMAK** may enhance the effects of alcohol, barbiturates, and other CNS depressants.

Some of the more serious central nervous system (CNS) reactions noted with the tricyclic antidepressants have occurred in short-term studies of cyclobenzaprine for indications other than muscle spasm associated with acute musculoskeletal conditions, and usually at doses somewhat greater than those recommended for skeletal muscle spasm. If clinically significant CNS symptoms develop, consider discontinuation of **PRIBEMAK.**

**Atropine-like reaction**

Because of its atropine-like action, **PRIBEMAK** should be used with caution in patients with a history of urinary retention, angle-closure glaucoma, increased intraocular pressure, and in patients taking anticholinergic medication.

The epileptogenic potential requires care in patients with a history of epilepsy.

**Information about excipients**

**PRIBEMAK** contains sucrose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

This medicinal product contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially "sodium-free".

**4.5 Interaction with other medicines and other forms of interaction**

Based on its structural similarity to tricyclic antidepressants, **PRIBEMAK** may have life-threatening interactions with MAO inhibitors (see **section 4.3**), may enhance the effects of alcohol, barbiturates, and other CNS depressants, may enhance the seizure risk in patients taking tramadol, or may block the antihypertensive action of guanethidine and similarly acting compounds.

Post-marketing cases of serotonin syndrome have been reported during combined use of cyclobenzaprine and other medicines, such as SSRIs, SNRIs, TCAs, tramadol, bupropion, meperidine, verapamil, or MAO inhibitors (see **section 4.4**).

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

Safety has not been established during pregnancy.

**Breastfeeding**

Safety has not been established during breastfeeding.

**Fertility**

No effects on fertility.

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

**PRIBEMAK** frequently causes dizziness and drowsiness; patients using **PRIBEMAK** should not drive or operate machinery.

**4.8 Undesirable effects**

*Summary of the safety profile*

The most common adverse effects were dry mouth, dizziness, fatigue, constipation, nausea, dyspepsia, and somnolence.

*Tabulated summary of adverse reactions*

| *System organ class* | Frequent | Less frequent | Frequency unknown |
|---|---|---|---|
| Blood and lymphatic system disorders | | | Purpura; bone marrow depression; leukopenia; eosinophilia; thrombocytopenia. |

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|---|---|---|---|
| Immune system disorders | | Anaphylaxis; angioedema. | |

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| Endocrine disorders | | | Inappropriate ADH syndrome |

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|---|---|---|---|
| Metabolism and nutrition disorders | | | Elevation and lowering of blood sugar levels; weight gain or loss. |
| Psychiatric disorders | | Depressed mood; abnormal sensations, anxiety; agitation; psychosis, abnormal thinking and dreaming; hallucinations; excitement; delusions; aggressive behaviour; paranoia; disturbance in attention. | |
| Nervous system disorders | Dizziness, somnolence, headache | Seizures, ataxia; vertigo; dysarthria; tremors; hypertonia; convulsions; muscle twitching; | |

| | | | |
|---|---|---|---|
| | | disorientation; insomnia; paraesthesia; diplopia; serotonin syndrome; neuroleptic malignant syndrome; decreased or increased libido; abnormal gait; peripheral neuropathy; Bell's palsy; alteration in EEG patterns; extrapyramidal symptoms; syncope. | |
| Eye disorders | Vision blurred | | |
| Ear and labyrinth disorders | Tinnitus | | |
| Cardiac disorders | | Tachycardia; dysrhythmia; vasodilatation; palpitation; hypotension; myocardial | |

| | | | |
|---|---|---|---|
| | | infarction; heart block; stroke; chest pain | |
| Vascular disorders | | | hypertension; oedema |
| Respiratory, thoracic and mediastinal disorders | | | Dyspnoea |
| Gastrointestinal disorders | Dry mouth; nausea; constipation; dyspepsia | Vomiting; anorexia; diarrhoea; gastrointestinal pain; gastritis; thirst; flatulence; oedema of the tongue; paralytic ileus, tongue discoloration; stomatitis; parotid swelling, ageusia, dysguesia | |
| Hepatobiliary disorders | | Hepatitis; jaundice; cholestasis; abnormal liver function and rare reports of hepatitis | |
| Skin and subcutaneous tissue disorders | | Sweating; photosensitization; alopecia; acne; pruritis; facial oedema; urticaria; | |

| | | | |
|---|---|---|---|
| | | rash | |
| Musculoskeletal and connective tissue disorders | | | Local weakness; myalgia |
| Renal and urinary disorders | | Urinary frequency and/or retention; impaired urination; dilatation of urinary tract | |
| Reproductive system and breast disorders | | | Impotence; testicular swelling; gynaecomastia; breast enlargement; galactorrhoea |
| General disorders and administration site conditions | | | Malaise |

*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 “Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

**4.9 Overdose**

The most common effects associated with cyclobenzaprine overdose are drowsiness and tachycardia. Less frequent manifestations include tremor, agitation, coma, ataxia, hypertension, slurred speech, confusion, dizziness, nausea, vomiting, and hallucinations. Rare but potentially critical manifestations of overdose are cardiac arrest, chest pain, cardiac dysrhythmias, severe hypotension, seizures, and

neuroleptic malignant syndrome. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of cyclobenzaprine toxicity. Other potential effects of overdosage include any of the symptoms listed in **section 4.8**.

Treatment is symptomatic and supportive. As management of overdose is complex and changing, it is recommended that the medical practitioner contact a poison control centre for current information on treatment. Signs and symptoms of toxicity may develop rapidly after cyclobenzaprine overdose, therefore hospital monitoring is required as soon as possible.

**Gastrointestinal Decontamination**

All patients suspected of an overdose with **PRIBEMAK** should receive gastrointestinal decontamination. This should include administration of activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage and emesis is contraindicated.

**Cardiovascular**

A maximal limb-lead QRS duration of 0,10 seconds may be the best indication of the severity of the overdose. Serum alkalinization, to a pH of 7,45 to 7,55, using intravenous sodium bicarbonate and hyperventilation (as needed), should be instituted for patients with dysrhythmias and/or QRS widening. A pH > 7,60 or a $pCO_2$ < 20 mmHg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium, or phenytoin. Type 1A and 1C antidysrhythmics are generally contraindicated (e.g., quinidine, disopyramide, and procainamide).

**CNS**

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines or, if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in close consultation with a poison control centre.

**Psychiatric Follow-Up**

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

**Paediatric Management**

The principles of management of child and adult overdosage are similar. It is strongly recommended that the physician contact the local poison control centre for specific paediatric treatment.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A 17.3 Medicines acting on muscular system. Others

ATC code: M03BX, Muscle relaxants, Centrally-acting agents

**Mechanism of action**

Cyclobenzaprine relieves skeletal muscle spasm of local origin without interfering with muscle function. Cyclobenzaprine has not been shown to be effective in muscle spasm due to central nervous system disease. In animal models, cyclobenzaprine reduced or abolished skeletal muscle hyperactivity. Animal studies indicate that cyclobenzaprine does not act at the neuromuscular junction or directly on skeletal muscle. Such studies show that cyclobenzaprine acts primarily within the central nervous system at the brain stem as opposed to the spinal cord level, although an overlapping action on the latter may contribute to its overall skeletal muscle relaxant activity. Evidence suggests that the net effect of cyclobenzaprine is a reduction of tonic somatic motor activity, influencing both gamma (γ) and alpha (α) motor systems. Pharmacological studies in animals demonstrated a similarity between the effects of cyclobenzaprine and the structurally related tricyclic antidepressants, including reserpine antagonism, norepinephrine potentiation, potent peripheral and central anticholinergic effects, and sedation. Cyclobenzaprine caused slight to moderate increase in heart rate in animals.

### 5.2 Pharmacokinetic properties

*Absorption*

Following single-dose administration of cyclobenzaprine 15 and 30 in healthy adult subjects, $C_{max}$, $AUC_{0\text{-}168h}$ and $AUC_{0\text{-}\infty}$ increased in an approximately dose-proportional manner from 15 mg to 30 mg. The time to peak plasma cyclobenzaprine concentration ($T_{max}$) was 7 to 8 hours for both doses of cyclobenzaprine.

A food effect study conducted in healthy adult subjects (n=15) utilizing a single dose of cyclobenzaprine 30 demonstrated a statistically significant increase in bioavailability when cyclobenzaprine 30 was given with food relative to the fasted state. There was a 35% increase in peak plasma cyclobenzaprine concentration ($C_{max}$) and a 20% increase in exposure ($AUC_{0\text{-}168h}$ and $AUC_{0\text{-}\infty}$) in the presence of food. No effect, however, was noted in $T_{max}$ or the shape of the mean

plasma cyclobenzaprine concentration versus time profile. Cyclobenzaprine in plasma was first detectable in both the fed and fasted states at 1.5 hours.

When the contents of cyclobenzaprine capsules were administered by sprinkling on applesauce, it was found to be bioequivalent to the same dose when administered as an intact capsule.

In a multiple-dose study utilizing cyclobenzaprine 30 administered once daily for 7 days in a group of healthy adult subjects, a 2.5-fold accumulation of plasma cyclobenzaprine levels was noted at steady-state.

*Biotransformation and Elimination*

Cyclobenzaprine is extensively metabolized and is excreted primarily as glucuronides via the kidney. Cytochromes P-450 3A4, 1A2, and, to a lesser extent, 2D6, mediate N-demethylation, one of the oxidative pathways for cyclobenzaprine. Cyclobenzaprine has an elimination half-life of 32 hours (range 8-37 hours); plasma clearance is 0.7 L/min following single-dose administration of cyclobenzaprine.

*Special populations*

*Elderly*

Although there were no notable differences in $C_{max}$ or $T_{max}$, cyclobenzaprine plasma AUC is increased by 40 % and the plasma half-life of cyclobenzaprine is prolonged in elderly subjects greater than 65 years of age (50 hours) after dosing with cyclobenzaprine compared to younger subjects 18 to 45 years of age (32 hours). Pharmacokinetic characteristics of cyclobenzaprine following multiple-dose administration of **PRIBEMAK** in the elderly were not evaluated.

*Hepatic Impairment*

In a pharmacokinetic study of immediate-release cyclobenzaprine in 16 subjects with hepatic impairment, both AUC and $C_{max}$ were approximately double the values seen in the healthy control group. The pharmacokinetics of cyclobenzaprine in subjects with severe hepatic impairment is not known.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sugar Spheres

Hypromellose

Isopropyl Alcohol

Methylene Chloride

Colloidal Silicon dioxide (Aerosil 200)

Ethyl Cellulose

**PRIBEMAK 15** contains gelatin, water, titanium dioxide, Sodium lauryl sulfate, D & C Yellow 10 (E104), FD & C Red 40 (E129) and FD & C Green 3 (E143)

**PRIBEMAK 30** contains gelatin, Sodium lauryl sulfate, water, titanium dioxide, FD & C Red 40 (E129), FD & C Yellow 6 (E110) and FD & C Blue 1 (E133)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

60 months from the manufacturing date for Blister pack.

24 months from the manufacturing date for HDPE container pack.

### 6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Do not store in a refrigerator.

KEEP OUT OF REACH OF CHILDREN

### 6.5 Nature and contents of container

**HDPE container:**

Capsules are packed in 60 ml round, white, HDPE container, 33 mm neck finish with 33 mm

polypropylene child resistant closure with Pulp and white printed Heat Seal Liner.

**Blister pack:**

Capsules are packed in aluminium foil laminated on one side and laminated to clear PVC on the other side. Pack sizes include 10s, 15s, 30s and 60s capsules.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

MACLEODS PHARMACEUTICALS SA (PTY) LTD

GROUND FLOOR, OFFICE BLOCK 1,

BASSONIA ESTATE OFFICE PARK (EAST),

1 CUSSONIA DRIVE,

BASSONIA ROCK EXT 12

ALBERTON

GAUTENG

**8. REGISTRATION NUMBERS**

**PRIBEMAK 15**: 57/17.3/0304

**PRIBEMAK 30**: 57/17.3/0305

**9. DATE OF FIRST AUTHORISATION**

20 May 2025

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



PM0247