### 1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

**SCHEDULING STATUS**

S2

## 1. NAME OF THE MEDICINE

**MENOGRAINE** tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of MENOGRAINE contains 25 µg of clonidine hydrochloride.

Contains sugar: Lactose monohydrate 30,118 mg

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Tablets

MENOGRAINE is a blue, round-shaped biconvex film-coated tablet, debossed with “12” on one side and plain on the other side.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

MENOGRAINE is indicated for the prevention of migraine.

### 4.2. Posology and method of administration

**Posology**

*Adults*

Take one tablet morning and night, increasing to three tablets twice daily if necessary.

**Method of administration**

For oral administration.

The coated tablet should not be chewed because of bad taste.

**4.3. Contraindications**

MENOGRAINE is contraindicated in:

- Patients with hypersensitivity to clonidine or to any of the ingredients as contained in MENOGRAINE (see section 6.1).
- Patients with porphyria.
- Patients with severe bradydysrhythmia resulting from either sick-sinus syndrome or AV block of 2nd or 3rd degree.

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

*Methylphenidate*

Serious adverse events, including sudden death, have been reported in concomitant use with methylphenidate. The safety of using methylphenidate in combination with MENOGRAINE has not been systematically evaluated.

*Depression*

MENOGRAINE should not be used in patients with a previous history of depressive illness, since further depressive episodes have been reported in such patients.

MENOGRAINE should be used with caution in patients with cerebrovascular disease, heart disease including myocardial infarction, coronary insufficiency, heart failure, renal impairment,

occlusive peripheral vascular disorder such as Raynaud's disease, polyneuropathy and constipation.

*Dysrhythmia*

Depending on the dose given, clonidine as contained in MENOGRAINE, can cause bradycardia. In patients with pre-existing cardiac conduction abnormalities, dysrhythmia have been observed after high doses of clonidine, as contained in MENOGRAINE.

*Withdrawal*

Withdrawal of MENOGRAINE therapy should be gradual as sudden discontinuation may cause rebound hypertension, sometimes severe. Caution should therefore be observed where antihypertensive medicines are being used, as potentiation of the hypotensive effect may occur. Provided the recommended MENOGRAINE dosage regimen is followed, no difficulty with hypotension should arise during the routine management of patients with migraine.
Patients should be instructed not to discontinue therapy without consulting their healthcare provider. Following sudden discontinuation of MENOGRAINE after prolonged treatment with high doses, agitation, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headache or nausea have been reported. When discontinuing therapy with MENOGRAINE, the medical practitioner should reduce the dose gradually over 2 to 4 days.

Symptoms of increased catecholamine release such as agitation, sweating, tachycardia, headache, and nausea may also occur. Beta-blockers can exacerbate the rebound hypertension and if MENOGRAINE is being given concurrently with a beta-blocking medicine, MENOGRAINE should not be discontinued until several days after the withdrawal of the beta-blocker.

Patients should be warned of the risk of missing a dose or stopping the medicine without

consulting their doctor and should carry a reserve supply of MENOGRAINE tablets.

*Anaesthesia*

Although hypotension may occur during anaesthesia in patients treated with clonidine, as contained in MENOGRAINE, clonidine should not be withdrawn, indeed, if necessary, it should be given intravenously during the operation to avoid the risk of rebound hypertension. Intravenous injection of clonidine should be given slowly to avoid a possible transient pressor effect especially in patients already receiving other antihypertensive medicines such as guanethidine or reserpine.

*Contact lenses*

Patients who wear contact lenses should be warned that treatment with clonidine, as contained in MENOGRAINE, may cause decreased lacrimation.

**Paediatric population**

The use and the safety of MENOGRAINE in children and adolescents under 18 years have insufficient evidence in randomized controlled trials and therefore cannot be recommended for use in this population.

*Excipients*

MENOGRAINE contains lactose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take MENOGRAINE.

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

*Antidepressants, vasodilators, diuretics and antihypertensive medicines*

The hypotensive effect may be antagonized by tricyclic antidepressants and enhanced by

vasodilators, diuretics or other antihypertensive medicines.

Orthostatic hypotension may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties.

It may be necessary to adjust the dosage of MENOGRAINE, if these medicines are administered concurrently.

*Beta-blockers and cardiac glycosides*

Beta-blockers can cause severe rebound hypertension.

Concomitant use of beta-blockers and/or cardiac glycosides can cause bradycardia or dysrhythmia (AV-block) in isolated cases.

It cannot be ruled out that concomitant administration of a beta-receptor blocker will cause or potentiate peripheral vascular disorders.

If during combined treatment with a beta-blocker there is need to interrupt or discontinue antihypertensive therapy, the beta-blocker must always be discontinued slowly first (reducing the dose gradually to avoid sympathetic hyperactivity) and then the clonidine, which should also be reduced gradually over several days if previously given in high doses.

*CNS depressants*

Central nervous system depressants can cause enhanced sedation.

Although there is no experience from clinical trials, the effect of tranquillisers, hypnotics or alcohol could theoretically be potentiated by clonidine, as contained in MENOGRAINE.

*Mirtazapine*

Substances with alpha$_2$-receptor blocking properties, such as mirtazapine, may abolish the alpha$_2$- receptor mediated effects of clonidine, as contained in MENOGRAINE in a dose-dependent manner.

## 4.6. Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established. Use with caution in pregnancy and lactation.

### Pregnancy

There is limited amount of data from the use of clonidine, as contained in MENOGRAINE, in pregnant women. As with all medicines, clonidine, as contained in MENOGRAINE, should not be used in pregnancy, especially the first trimester.

In animal studies involving doses higher than the equivalent maximum therapeutic dose in man, effects on foetal development were only seen in one species. Foetal malformations did not occur.

Careful monitoring of mother and child is recommended.

Clonidine, as contained in MENOGRAINE, passes the placental barrier and may lower the heart rate of the foetus. Postpartum, a transient rise in blood pressure in the new-born cannot be excluded.

There is no adequate experience regarding the long-term effects of prenatal exposure.

### Breastfeeding

Clonidine, as contained in MENOGRAINE, is excreted in human milk. However, there is insufficient information on the effect on new-borns. The use of clonidine is therefore not recommended during breast feeding.

### Fertility

No clinical studies on the effect on human fertility have been conducted with clonidine. Non-clinical studies with clonidine, as contained in MENOGRAINE indicate no direct or indirect harmful effects with respect to the fertility index.

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

MENOGRAINE has a moderate influence.

MENOGRAINE may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressant medicines. Patients should be warned not to take charge of vehicles or machinery or perform potentially hazardous tasks where loss of concentration may lead to accidents.

## 4.8. Undesirable effects

*a) Summary of the safety profile*

Drowsiness, dry mouth, dizziness, and headache commonly occur during the initial stages of therapy with MENOGRAINE.

Most adverse effects are mild and tend to diminish with continued therapy.

*b) Tabulated list of adverse reactions*

| **System organ class** | **Frequent** | **Less frequent** | **Frequency unknown** (cannot be estimated from the available data) |
|---|---|---|---|
| **Endocrine disorders** | | Gynaecomastia, | |
| **Metabolism and nutrition disorders** | | | Anorexia, fluid retention |
| **Psychiatric disorders** | Depression, sleep disturbances | Hallucination | Anxiety, vivid dreams, loss of libido, confusional state, delusional perception |
| **Nervous system disorders** | Drowsiness, dizziness, headache, sedation | Paraesthesia | |
| **Eye disorders** | | | Dry, itching, or burning sensations in the eye, accommodation disorder, decreased lacrimation |
| **Cardiac disorders** | | | Bradycardia sinus, bradycardia with atrioventricular block, other electro cardiographic disturbances, heart failure, |

| | | | |
|---|---|---|---|
| **Vascular disorders** | Slight orthostatic hypotension | Raynaud's syndrome | |
| **Respiratory, thoracic and mediastinal disorders** | | | Nasal dryness |
| **Gastrointestinal disorders** | Constipation, dry mouth, nausea, salivary gland pain, vomiting | | Parotid pain, colonic pseudo-obstruction |
| **Skin and subcutaneous tissue disorders** | | | Rashes and pruritus, alopecia, urticaria |
| **Musculoskeletal and connective tissue disorders** | | Cramps | |
| **Renal and urinary disorders** | | | Urinary retention or incontinence |
| **Reproductive system and breast disorders** | | | Impotence, erectile dysfunction |
| **General disorders and administrative site conditions** | Fatigue | | Malaise |
| **Investigations** | | Transient abnormalities in liver function tests, increases in blood pressure and transient hyperglycaemia | |

c) *Description of selected adverse reactions*

*Metabolism and nutrition disorders*

Fluid retention may occur and is usually transient but may be responsible for a reduction in the hypotensive effect during continued treatment.

*Investigations*

Large doses have been associated with initial increases in blood pressure and transient hyperglycaemia, although these do not persist during continued therapy.

*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 providers 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

**Aspen Pharmacare:**

**E-mail:** Drugsafety@aspenpharma.com

**Tel:** 0800 118 088

**4.9. Overdose**

**Symptoms**

Symptoms of overdosage are due to a generalised sympathetic depression and include pupillary constriction, somnolence including coma, transient hypertension, bradycardia, hypothermia, sedation, miosis, respiratory depression including apnoea, convulsions, occasionally vomiting and dryness of the mouth.

**Treatment**

Treatment is supportive and symptomatic. An alpha adreno-receptor blocking medicine may be given if necessary.

Administration of activated charcoal should be performed where appropriate.

Supportive care may include atropine sulfate for symptomatic bradycardia, and intravenous fluids and/or inotropic sympathomimetic medicines for hypotension. Severe persistent hypertension may require correction with alpha-adrenoceptor blocking medicines.

Naloxone may be a useful adjunct for the management of clonidine-induced respiratory depression.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Category and class: A 7.3 Migraine preparations

Pharmacotherapeutic group: Other antimigraine preparations

ATC code: N02CX

*Mechanism of action*

Clonidine hydrochloride has both central and peripheral action on $\alpha_2$ adrenergic receptors. It reduces vascular responses to vasoconstrictor as well as vasodilator stimuli.

### 5.2. Pharmacokinetic properties

**Absorption**

Clonidine is well absorbed after oral administration, and bioavailability is nearly 100 %.

**Distribution**

The peak concentration in plasma and the maximal hypotensive effect are observed 1 to 3 hours after an oral dose.

**Biotransformation**

About half of an administered dose can be recovered unchanged in the urine, and the half-life of clonidine may increase with renal failure.

**Elimination**

The elimination half-life of clonidine ranges from 6 to 24 hours, with a mean of about 12 hours.

***Special population***

*Paediatric population*

There were also two small paediatric studies in migraine, neither of which demonstrated efficacy. In the paediatric studies the most frequent adverse events were drowsiness, dry mouth, headache, dizziness and insomnia. These adverse events might have serious impact on daily functioning in paediatric patients.

Overall, the safety and efficacy of clonidine in children and adolescents have not been established.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Lactose monohydrate, magnesium stearate, microcrystalline cellulose, Opadry 04B505004 Blue (hypromellose, indigo carmine aluminium lake, macrogol 400, titanium dioxide), sodium starch glycollate, starch maize, purified talc.

### 6.2. Incompatibilities

Not applicable.

### 6.3. Shelf life

24 months.

### 6.4. Special precautions for storage

Store at or below 25 °C.

Keep container tightly closed.

Protect from light.

Keep in original packaging until required for use.

**6.5 Nature and contents of container**

Packs of 30 and 100 tablets in white polypropylene securitainers sealed together with a package insert, foam insert or rayon, using a round white, flat-topped low-density polyethylene (LDPE) closure.

Packs of 30 and 100 tablets in white, opaque, round high-density polyethylene (HDPE) containers, sealed together with white absorbent cotton using a white, opaque polypropylene fine-ribbed screw cap.

Packs of 20 tablets in polyvinyl chloride (PVC) blister strips sealed using aluminium foil. The blister strips are packed together with a package insert, into pre-printed cardboard unit cartons.

Not all packs and pack sizes are necessarily marketed.

**6.6. Special precautions for disposal**

No special requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

**8. REGISTRATION NUMBER**

M/7.3/41

**9. DATE OF FIRST AUTHORISATION**

04 April 1986

## 10. DATE OF REVISION OF TEXT

24 November 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

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