

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1. Name of the medicinal product

Clonnirit®

### 2. Qualitative and quantitative composition

Each tablet contains clonidine hydrochloride 25 micrograms.

Excipients:

Each tablet contains approximately 18 mg lactose.

For full list of excipients, see Section 6.1.

### 3. Pharmaceutical form

Tablets

Small round pale blue tablets.

### 4. Clinical particulars

#### 4.1 Therapeutic indications

Prophylaxis of migraine and recurrent vascular headache, but not acute attacks. Treatment of menopausal flushing.

#### 4.2 Posology and method of administration

##### **Adults:**

Initially 2 tablets twice daily. If after two weeks there has been no remission, increase to 3 tablets twice daily.

The duration of treatment depends upon the severity of the condition.

If symptoms continue to occur the patient should be informed that it may take 2-4 weeks until Clonnirit is fully effective.

##### **Elderly:**

No specific information on the use of this product in the elderly is available.

Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

##### **Paediatric Population:**

There is insufficient evidence for the application of clonidine in children and adolescents younger than 18 years. Therefore the use of clonidine is not recommended in paediatric subjects under 18 years.

##### **Patients with renal impairment**

Clonnirit should be used with caution in patients with renal insufficiency. Careful monitoring of blood pressure is required.

##### Method of administration

Per Os

#### 4.3 Contraindications

Clonnirit should not be used in patients with severe bradyarrhythmia resulting from either sick-sinus syndrome or AV block of 2nd or 3rd degree, or in patients with hypersensitivity to the active substance, clonidine, or to any of the excipients listed in section 6.1.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to section 4.4 Special warnings and precautions for use) the use of this product is contraindicated.

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

Clonnirit should be used with caution in patients with cerebrovascular disease, coronary insufficiency, heart failure, occlusive peripheral vascular disorders, such as Raynaud's disease, polyneuropathy, constipation or those with a history of depression.

At doses higher than those recommended above, clonidine is an effective antihypertensive agent. Caution should therefore be observed where antihypertensive agents are being used, as potentiation of the hypotensive effect may occur. Provided the recommended Clonnirit dosage regimen is followed, no difficulty with hypotension should arise during the routine management of patients with either migraine or menopausal flushing.

Depending on the dose given, clonidine hydrochloride can cause bradycardia. In patients with pre-existing cardiac conduction abnormalities, arrhythmias have been observed after high doses of clonidine hydrochloride.

Patients with renal failure require extreme care (See Section 4.2).

Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of clonidine hydrochloride 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 Clonnirit, the physician should reduce the dose gradually over 2-4 days.

Patients who wear contact lenses should be warned that treatment with Clonnirit may cause decreased lacrimation.

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

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

This medicine contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Concurrent administration of antihypertensive agents, vasodilators or diuretics, may lead to an increased hypotensive effect.

Substances with  $\alpha_2$ -receptor blocking properties, such as mirtazapine, may abolish the  $\alpha_2$ -receptor mediated effects of clonidine in a dose-dependent manner.

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 a 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 Clonnirit, which should also be reduced gradually over several days if previously given in high doses.

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

As the effects of clonidine can be antagonised by tricyclic anti-depressants, it may be necessary to adjust the dosage of Clonnirit, if these agents are administered concurrently.

Although there is no experience from clinical trials, the effect of tranquillisers, hypnotics or alcohol could theoretically be potentiated by Clonnirit.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

There are limited amount of data from the use of clonidine in pregnant women. As with all medicines, Clonnirit should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh any possible risk to the foetus.

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 passes the placental barrier and may lower the heart rate of the foetus. Post partum a transient rise in blood pressure in the newborn cannot be excluded.

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

##### Breast-feeding

Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. The use of Clonnirit 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 indicate no direct or indirect harmful effects with respect to the fertility index.

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

No studies on the effects on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects such as dizziness, sedation and accommodation disorder during treatment with Clonnirit. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

#### **4.8 Undesirable effects**

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

Adverse events have been ranked under headings of frequency using the following convention: very common ( $\geq 1/10$ ), common ( $\geq 1/100, < 1/10$ ), uncommon ( $\geq 1/1,000, < 1/100$ ), rare ( $\geq 1/10,000, < 1/1,000$ ), very rare ( $< 1/10,000$ ) and unknown (cannot be calculated from the available data).

Cardiac disorders:

Bradyarrhythmia: not known

sinus bradycardia: uncommon

AV-block: rare

Nervous system disorders:  
Dizziness, Sedation: very common  
Headache: common  
Paraesthesia: uncommon

Eye disorders:  
Lacrimation decreased: rare.  
Accommodation disorder: not known

Respiratory, thoracic and mediastinal disorders:  
Nasal dryness: rare

Gastrointestinal disorders:  
Dry mouth: very common  
Constipation, Nausea, Salivary gland pain, Vomiting: common  
Colonic pseudo-obstruction: rare

Skin and subcutaneous tissue disorders:  
Pruritus, Rash, Urticaria: uncommon  
Alopecia: rare

Vascular disorders:  
Orthostatic hypotension: very common  
Raynaud's phenomenon: uncommon

General disorders and administration site conditions:  
Fatigue: common  
Malaise: uncommon

Reproductive system and breast disorders:  
Erectile dysfunction: common

Endocrine disorders:  
Gynaecomastia: rare

Psychiatric disorders:  
Sleep disorder, depression: common  
Hallucination, delusional perception, nightmare: uncommon  
Confusional state, libido decreased: not known

Investigations:  
Blood glucose increased: rare

#### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit / risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<https://sideeffects.health.gov.il/>

#### **4.9 Overdose**

##### *Symptoms:*

Manifestations of intoxication are due to a generalised sympathetic depression and include pupillary constriction, somnolence including coma, hypotension, orthostatic hypotension,

bradycardia, hypothermia, respiratory depression including apnoea, occasionally vomiting, very occasionally hypertension, dryness of the mouth.

*Treatment:*

There is no specific antidote for clonidine overdose. 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 agents for hypotension. Severe persistent hypertension may require correction with alpha-adrenoceptor blocking drugs.

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

## **5. Pharmacological properties**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antimigraine preparations  
ATC code: N02C X02

Clonidine is an antihypertensive agent, which acts centrally by stimulating alpha<sub>2</sub>-adrenergic receptors and producing a reduction in sympathetic tone, resulting in a fall in diastolic and systolic blood pressure and a reduction in heart rate.

Treatment with Clonnirit diminishes the responsiveness of peripheral vessels to constrictor and dilator stimuli, thereby preventing the vascular changes associated with migraine. The same direct action on peripheral vessels moderates the vascular changes associated with menopausal flushing.

#### Paediatric population

The efficacy of clonidine in the treatment of hypertension has been investigated in five clinical studies in paediatric patients. The efficacy data confirms the properties of clonidine in reduction of systolic and diastolic blood pressure. However, due to limited data and methodological insufficiencies, no definitive conclusion can be drawn on the use of clonidine for hypertensive children.

The efficacy of clonidine has also been investigated in a few clinical studies with paediatric patients with ADHD, Tourette syndrome and stuttering. The efficacy of clonidine in these conditions has not been demonstrated.

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 (see section 4.2).

### **5.2 Pharmacokinetic properties**

#### Absorption and distribution

The pharmacokinetics of clonidine is dose-proportional in the range of 75-300 micrograms; over this range, dose linearity has not been fully demonstrated.

Clonidine, the active ingredient of Clonnirit, is highly absorbed and undergoes a minor first pass effect.

Peak plasma concentrations are reached within 1-3 h after oral administration. The plasma protein binding is 30-40 %. Clonidine is rapidly and extensively distributed into tissues and crosses the blood-brain barrier, as well as the placental barrier. Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns.

#### Biotransformation and elimination

The terminal elimination half-life of clonidine has been found to range from 5 to 25.5 hours. It can be prolonged in patients with severely impaired renal function up to 41 hours.

About 70 % of the dose administered is excreted with the urine mainly in form of the unchanged parent drug (40-60 % of the dose). The main metabolite p-hydroxy-clonidine is pharmacologically inactive. Approximately 20% of the total amount is excreted with the faeces. There is no definitive data about food or race effects on the pharmacokinetics of clonidine.

The antihypertensive effect is reached at plasma concentrations between about 0.2 and 2.0 ng/ml in patients with normal renal function. The hypotensive effect is attenuated or decreases with plasma concentrations above 2.0 ng/ml.

#### **5.3 Preclinical safety data**

There are no preclinical data of relevance to the prescriber, which are additional to that already included in other sections of the SmPC.

### **6. Pharmaceutical particulars**

#### **6.1 List of excipients**

Starch corn, lactose, calcium phosphate dibasic, starch soluble, silicon dioxide colloidal, povidone K25, magnesium stearate, indigotine blue (E132).

#### **6.2 Incompatibilities**

Not applicable.

#### **6.3 Shelf life**

The expiry date of the product is indicated on the packaging materials.

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

Store below 25°C

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

Packs of 30 tablets in blisters.

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

No special requirements.

### **7. Manufacturer and registration holder:**

Rafa Laboratories Ltd., P.O.Box 405, Jerusalem 9100301

Registration number: 044 54 22183

Revised in July 2023 according to MOHs guidelines.