SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clonidine hydrochloride 50micrograms/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of oral solution contains 50micrograms clonidine hydrochloride.

Excipients with known effect:

Each 5ml of oral solution contains 9mg methyl parahydroxybenzoate (E218).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Oral solution

A clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

a) The prophylactic management of migraine or recurrent vascular headache.

b) The management of vasomotor conditions commonly associated with the menopause and characterised by flushing.

4.2 Posology and method of administration

Adults:

Initially 5ml (50micrograms) twice daily. If after two weeks there has been no remission, increase to 7.5ml (75micrograms) 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 Clonidine hydrochloride 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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Clonidine hydrochloride 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 Clonidine hydrochloride 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 Clonidine hydrochloride, the physician should reduce the dose gradually over 2-4 days.

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

The use and the safety of clonidine in children and adolescents has little supporting evidence in randomized controlled trials and therefore cannot 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.

Excipients warnings

This product contains methyl parahydroxybenzoate (E218), which may cause allergic reactions (possibly delayed).

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 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 hydrochloride, 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 Clonidine hydrochloride, 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 Clonidine hydrochloride.

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, Clonidine hydrochloride 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.

Lactation

Clonidine is excreted in human milk. However, there is insufficient information on the effect on newborns. The use of Clonidine hydrochloride 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 Clonidine hydrochloride. 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	> 1/10
Common	> 1/100, <1/10
Uncommon	>1/1000, <1/100
Rare	>1/10000, <1/1000
Very rare	<1/10000
Not known	Cannot be estimated from the available data

<u>Endocrine disorders:</u>	
Gynaecomastia	rare
<u>Psychiatric disorders:</u>	
confusional state	not known

delusional perception	uncommon
depression	common
hallucination	uncommon
libido decreased	not known
nightmare	uncommon
sleep disorder	common
Nervous system disorders:	
dizziness	very common
headache	common
paraesthesia	uncommon
sedation	very common
Eye disorder:	
accommodation disorder	not known
lacrimation decreased	rare
Cardiac disorders:	
atrioventricular block	rare
bradyarrhythmia	not known
sinus bradycardia	uncommon
Vascular disorders:	
orthostatic hypotension	very common
Raynaud's phenomenon	uncommon
Respiratory, thoracic and mediastinal disorders:	
nasal dryness	rare
Gastrointestinal disorders:	
colonic pseudo-obstruction	rare
constipation	common
dry mouth	very common
nausea	common
salivary gland pain	common
vomiting	common

Skin and subcutaneous tissue disorders:	
Alopecia	rare
Pruritus	uncommon
Rash	uncommon
Urticaria	uncommon
Reproductive system and breast disorders:	
erectile dysfunction	common
General disorders and administration site conditions:	
Fatigue	common
Malaise	uncommon
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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms:

Manifestations of intoxication are due to 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

Clonidine is an antihypertensive agent which acts centrally by stimulating alpha$_2$-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 Clonidine hydrochloride 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.

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 75-300micrograms; over this range, dose linearity has not been fully demonstrated.

Clonidine, the active ingredient of Clonidine hydrochloride, 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.

Metabolism 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 SPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Methyl parahydroxybenzoate (E218)

Sodium dihydrogen phosphate monohydrate

Disodium hydrogen phosphate anhydrous

Sucralose (E955)

Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months

Discard 30 days after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

Do not refrigerate or freeze.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bottle: Type III amber glass bottle

Closure: Tamper evident, child resistant white plastic cap consists of polypropylene inner, polyethylene outer, expanded polyethylene (EPE) liner.

Dosing Device: 10ml polypropylene oral syringe with 0.5ml graduation mark and an adaptor for the syringe.

Pack size: 100ml

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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