SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clonidine Macure 150 micrograms/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains clonidine hydrochloride 150 micrograms. For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Solution for injection. Clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clonidine Macure is indicated for the treatment of hypertensive crises.

4.2 Posology and method of administration

Adults, including the elderly:

In hypertensive crises 150 to 300 micrograms (1 to 2 ampoules) should be given by slow intravenous injection. This dose may be repeated up to a maximum of

750 micrograms (5 ampoules) in a 24-hour period.

Patients undergoing anaesthesia should continue their Clonidine Macure treatment before, during and after anaesthesia using oral or intravenous administration according to individual circumstances.

Intravenous injection of Clonidine Macure should be given slowly over 10-15 minutes to avoid a possible transient pressor effect.

Clonidine Macure injection solution is compatible with 0.9% sodium chloride solution and with 5% Dextrose solution.

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.

Renal insufficiency:

Dosage must be adjusted

- according to the individual antihypertensive response which can show high variability in patients with renal insufficiency
- according to the degree of renal impairment

4.3 Contraindications

Clonidine Macure should not be used in children (please refer to section 4.4 Special Warnings and Precautions for Use) or in patients with known hypersensitivity to the active ingredient or other components of the product, and in patients with severe bradyarrhythmia resulting from either sick sinus syndrome or AV block of 2nd or 3rd degree.

4.4 Special warnings and precautions for use

Clonidine should only be used with caution in patients with depression or a history thereof, with Raynaud's disease or other peripheral vascular occlusive disease.

The product should only be used with caution in patients with cerebrovascular or coronary insufficiency. Clonidine Macure should be used with caution in patients with mild to moderate bradyarrhythmia such as low sinus rhythm, and with polyneuropathy or constipation.

As with other antihypertensive drugs, treatment with Clonidine Macure should be monitored particularly carefully in patients with heart failure.

In hypertension caused by phaeochromocytoma no therapeutic effect of Clonidine Macure can be expected.

Clonidine, the active ingredient of Clonidine Macure, and its metabolites, are extensively excreted in urine. Dosage must be adjusted to the individual antihypertensive response, which can show high variability in patients with renal insufficiency (see Section 4.2 Posology and Method of Administration); careful monitoring is required.

Since only a minimal amount of clonidine is removed during routine haemodialysis, there is no need to give supplemental clonidine following dialysis.

Patients who wear contact lenses should be warned that treatment with Clonidine Macure 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.

4.5 Interaction with other medicinal products and other forms of interaction

The reduction in blood pressure induced by clonidine can be further potentiated by concurrent administration of other hypotensive agents. This can be of therapeutic use in the case of other antihypertensive agents such as diuretics, vasodilators, beta-receptor blockers, calcium antagonists and ACE-inhibitors, but the effect of alpha1-blockers is unpredictable.

The antihypertensive effect of clonidine may be reduced or abolished and orthostatic hypotension may be provoked or aggravated by concomitant administration of tricyclic antidepressants or neuroleptics with alpha-receptor blocking properties.

Substances which raise blood pressure or induce a sodium ion (Na^+) and water retaining effect such as non-steroidal anti-inflammatory agents can reduce the therapeutic effect of clonidine.

Substances with alpha2-receptor blocking properties, such as mirtazapine, may abolish the alpha2-receptor mediated effects of clonidine in a dose-dependent manner.Concomitant administration of substances with a negative chronotropic or dromotropic effect such as beta-receptor blockers or digitalis glycosides can cause or potentiate bradycardic rhythm disturbances.

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

Based on observations in patients in a state of alcoholic delirium it has been suggested that high intravenous doses of clonidine may increase the arrhythmogenic potential (QT-prolongation, ventricular fibrillation) of high intravenous doses of haloperidol. Causal relationship and relevance for antihypertensive treatment have not been established.

The effects of centrally depressant substances or alcohol can be potentiated by clonidine.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is limited amount of data from the use of clonidine in pregnant women.

This product should only be used in pregnancy if considered essential by the physician. Careful monitoring of mother and child are 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 new-born cannot be excluded.

Non-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.

Lactation

Clonidine is excreted in human milk. However, there is insufficient information on the effect on new-borns. The use of Clonidine Macure is therefore not recommended during breastfeeding.

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 Macure. 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 disorders:	
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

Fluid retention and abnormal liver function tests have been reported occasionally. Two cases of hepatitis have also been reported.

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 at:

www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms:

Manifestations of intoxication are due to a generalised sympathetic depression and include pupillary constriction, lethargy, bradycardia, hypotension, hypothermia, somnolence including coma and respiratory depression including apnoea. Paradoxical hypertension caused by stimulation of peripheral alpha1-receptors may occur.

Transient hypertension may be seen if the total dose is over 10 mg.

Treatment:

There is no specific antidote for clonidine overdose. Administration of activated charcoal should be performed where appropriate.

Supportive care may include atropine sulphate 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: Centrally acting antihypertensives, ATC Code C02AC01.

Clonidine acts primarily on the central nervous system, resulting in reduced sympathetic outflow and a decrease in peripheral resistance, renal vascular resistance, heart rate and blood pressure. Renal blood flow and glomerular filtration rate remain essentially unchanged. Normal postural reflexes are intact and therefore orthostatic symptoms are mild and infrequent. During long-term therapy, cardiac output tends to return to control values, while peripheral resistance remains decreased. Slowing of the pulse has been observed in most patients given clonidine, but the drug does not alter normal haemodynamic response to exercise.

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 weredrowsiness, 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

The pharmacokinetics of clonidine is dose proportional in the range of 100- 600 micrograms. Clonidine, the active ingredient of Clonidine Macure, is well

absorbed and no first pass effect exists. It is rapidly and extensively distributed into tissues and crosses the blood-brain barrier as well as the placental barrier. The plasma protein binding is 30-40%.

The mean plasma half-life of clonidine is 13 hours ranging between 10 and 20 hours. The half-life does not depend on the sex or race of the patient but 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 the form of the unchanged parent drug (40-60%). The main metabolite p-hydroxy-clonidine is pharmacologically inactive. Approximately 20% of the total amount is excreted with the faeces.

The antihypertensive effect is reached at plasma concentrations between about 0.2 and 1.5ng/ml in patients with normal excretory function. A further rise in the plasma levels will not enhance the antihypertensive effect.

5.3 Preclinical safety data

Not applicable.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Hydrochloric acid

Water for injections

6.2 Incompatibilities

None known.

6.3 Shelf life

Unopened: 36 months.

Once opened, use immediately and discard any unused contents.

Chemical and physical in-use stability of the solution diluted in 5% glucose or 0.9% sodium chloride has been demonstrated for 24 hours in ambient conditions.

6.4 Special precautions for storage

This medicine does not require any special storage conditions.

6.5 Nature and contents of container

1 ml colourless glass (Ph. Eur. Type I) ampoules, marketed in packs of 5.

6.6 Special precautions for disposal

For single use only. Discard any unused contents.

7 MARKETING AUTHORISATION HOLDER

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138-142 Holborn
London EC1N 2SW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 54594/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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