

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Dixarit Tablets 25 micrograms

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains clonidine hydrochloride 25 micrograms.

Excipients with known effect: Each tablet contains 16.85 mg lactose and 20.388 mg sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated tablet

Blue, biconvex, sugar-coated tablets.

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 (including elderly patients):

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 Dixarit is fully effective.

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

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

4.3 Contraindications

Dixarit 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 known hypersensitivity to the active ingredient, clonidine, or other components of the product.

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 the product is contraindicated.

4.4 Special warnings and precautions for use

Dixarit 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 patients with depression or a history thereof.

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 Dixarit 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, Dixarit can cause bradycardia. In patients with pre-existing cardiac conduction abnormalities, arrhythmias have been observed after high doses of Dixarit.

Patients with renal failure require extreme care (see section 4.2 Posology and Method of Administration).

Patients should be instructed not to discontinue therapy without consulting their physician. Following sudden discontinuation of Dixarit after prolonged treatment with high doses, restlessness, palpitations, rapid rise in blood pressure, nervousness, tremor, headache or nausea have been reported. When discontinuing therapy with Dixarit, the physician should reduce the dose gradually over 2-4 days.

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

The use and the safety of clonidine in children and adolescent has little supporting evidence in randomized controlled trials and therefore can not be recommended for use in this population.

In particular, when clonidine is used off-label concomitantly with methylphenidate in children with ADHD, serious adverse reactions, including death, have been observed. Therefore, clonidine in this combination is not recommended.

This product contains 101.1 mg of lactose per maximum daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

This product contains 122.3 mg sucrose per maximum daily dose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Clonidine is available for the management of hypertension as Catapres Tablets (100 micrograms) and Ampoules (150 micrograms in 1 ml). Where Catapres is already being used Dixarit therapy is obviously not indicated.

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 α_2 -receptor blocking properties, such as mirtazapine, may abolish the α_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 Dixarit, 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 Dixarit, 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 Dixarit.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of clonidine in pregnant women. Dixarit should not be used in pregnancy especially the first trimester, unless considered essential by the physician, and 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 Dixarit 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 Dixarit. 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	$\geq 1/10000, < 1/1000$
Very rare	$< 1/10000$
Not known	Cannot be estimated from the available data

Endocrine disorders:

Gynaecomastia	rare
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Psychiatric disorders:

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
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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
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General disorders and administration site conditions:

Fatigue	common
Malaise	uncommon

Investigations:

blood glucose increased	rare
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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 HPRA

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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:

Gastric lavage and/or administration of activated charcoal should be performed where appropriate. In most cases all that is required are general supportive measures.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

Clonidine is an antihypertensive agent which acts centrally by stimulating α_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 Dixarit 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 75-300 micrograms; over this range, dose linearity has not been fully demonstrated. Clonidine, the active ingredient of Dixarit, 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

Tablet core:

Calcium hydrogen phosphate, anhydrous
Lactose Monohydrate
Maize starch
Colloidal anhydrous silica
Povidone
Maize starch, soluble
Indigo carmine (E132)
Magnesium stearate

Tablet coating:

Povidone
Sucrose
Talc
Acacia
Titanium Dioxide (E171)
Indigo carmine (E132)
Macrogol
Carnauba wax
White beeswax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C.

Keep the blisters in the outer carton.

6.5 Nature and contents of container

PVC/aluminium blister packs of 84, 100, 112.

Currently the 112 pack is the only marketed pack.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Boehringer Ingelheim Limited
Ellesfield Avenue
Bracknell
Berkshire RG12 8YS
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8 MARKETING AUTHORISATION NUMBER

PA 0007/032/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 May 1987

Date of last renewal: 01 November 2005

10 DATE OF REVISION OF THE TEXT

July 2015