New Zealand Datasheet

Name of Medicine

DIXARIT®

Clonidine hydrochloride

Presentation

Tablet: 25 mcg, blue, biconvex, sugar coated.

Note: DIXARIT contains the same active ingredient as the antihypertensive agent CATAPRES, but in only one-sixth the quantity (25 micrograms compared with 150 micrograms). It follows that the two agents will not need to be used together in the same patient.

Uses

Actions

DIXARIT is a centrally acting α_2-agonist. The central inhibiting effect on nor-adrenergic neurotransmission generally dominates the peripheral excitatory α_2-effect.

In the prophylaxis of migraine, based on observations that vascular responsiveness is reduced after long-term administration of low doses of clonidine, a hypothesis of a peripheral mode of action has been put forward. The reduced responsiveness of the vessels to adrenergic stimuli due to clonidine possibly also plays a significant role in the reduction of menopausal hot flushes. Central as well as peripheral mode of action are discussed as affecting climateric complaints, e.g. reduced nor-adrenergic activity in the hypothalamus and changes in central hormone secretion.

Pharmacokinetics

Absorption and distribution

The pharmacokinetics of clonidine is dose-proportional in the range of 75 - 300 mcg. Clonidine, the active ingredient of DIXARIT, is well 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 eliminationThe 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. The pharmacokinetics of clonidine is not influenced by food nor by the race of the patient.

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

Indications

The prophylactic management of migraine or recurrent vascular headaches in adult patients.

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

Dosage and Administration

Adults (including elderly patients):
Therapy should be started with 1 tablet 2 times daily (morning and evening).

If there is no relief after two weeks the dosage can be gradually increased to 3 tablets 2 times daily.

Duration of treatment will depend on the frequency and severity of attacks. It may take 2 - 4 weeks until DIXARIT is fully effective.

Note: DIXARIT is not suitable for clearing acute migraine headaches.

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

Contraindications

DIXARIT should not be used 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 blocks of 2nd or 3rd degree.

In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to Warnings and Precautions) the use of the product is contraindicated.

Warnings and Precautions

DIXARIT should be used with caution in patients with mild to moderate bradyarrhythmia, such as low sinus rhythm, with disorders of cerebral or peripheral perfusion, depression, polyneuropathy and constipation.

Clonidine, the active ingredient of DIXARIT, and its metabolites are extensively excreted with the urine. DIXARIT should therefore be used with caution in patients with renal insufficiency (see Dosage and Administration.

As with other antihypertensive drugs, treatment with DIXARIT should be monitored particularly carefully in patients with heart failure or severe coronary disease.

In patients who have developed localised skin reaction to CATAPRES TTS transdermal patch, substitution of oral clonidine therapy may be associated with the development of a generalised rash.

If long-term treatment with a beta-receptor blocker has to be interrupted, then the beta-receptor blocker should first be phased out gradually and then clonidine.

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, headaches or nausea have been reported. When discontinuing therapy with DIXARIT, the physician should reduce the dose gradually over 2 – 4 days. An excessive rise in blood pressure following discontinuation of DIXARIT therapy can be reversed by intravenous phentolamine or tolazoline (see Interactions)

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 ADHS, 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 recommended daily dose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia should not take this medicine.

This product contains 122.3 mg of Sucrose per maximum recommended daily dose. Patients with the rare hereditary condition of fructose intolerance should not take this medicine.

Use in Pregnancy
There are limited amount of data from the use of clonidine in pregnant women. During pregnancy, DIXARIT, as any drug, should only be administered if the benefit justifies any possible risks to the foetus. Careful monitoring of mother and child is recommended. Clonidine passes the placenta barrier and may lower the heart rate of the foetus. There is no adequate experience regarding long-term effects of prenatal exposure.

During pregnancy the oral forms of clonidine should be preferred. Intravenous injection of clonidine should be avoided.

Non-clinical studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see Further Information - Toxicology). Post partum a transient rise in blood pressure in the newborn cannot be excluded

Use in 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 (see Further Information - Toxicology).

Affects on Ability to Drive or Operate Machinery
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. Therefore, caution should be recommended when driving a car or operating machinery. If patients experience the above mentioned side effects they should avoid potentially hazardous tasks such as driving or operating machinery.

Adverse Effects
Most adverse effects are mild and tend to diminish with continued therapy. Frequent side effects are dryness of mouth, sedation and reduction of blood pressure.

Endocrine disorders:
gynaecomastia

Psychiatric disorders:
confusional state, delusional perception, depression, hallucination, libido decreased, nightmare, sleep disorder

Nervous system disorders:
dizziness, headache, paraesthesia, sedation

Eye disorder:
accommodation disorder, lacrimation decreased

Cardiac disorders:
atrioventricular block, bradyarrhythmia, sinus bradycardia

Vascular disorders:
orthostatic hypotension, Raynaud's phenomenon

Respiratory, thoracic and mediastinal disorders:
nasal dryness

Gastrointestinal disorders:
colonic pseudo-obstruction, constipation, dry mouth, nausea, salivary gland pain, vomiting

Skin and subcutaneous tissue disorders:
alopecia, pruritus, rash, urticaria

Reproductive system and breast disorders:
erectile dysfunction

General disorders and administration site conditions:
fatigue, malaise

Investigations:
blood glucose increased

Interactions

If DIXARIT is administered concomitantly with agents such as diuretics, vasodilators, beta-receptor blockers, calcium antagonists, ACE-inhibitors, their hypotensive effect can be potentiated.

Substances with alpha$_2$-receptor blocking properties such as phentolamine or tolazoline may abolish the alpha$_2$-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 disorders. Studies with combined administration of clonidine and beta-receptor blockers have shown that if treatment is to be discontinued, the dose of the beta-receptor blocker must always be slowly diminished first followed by the clonidine.

Orthostatic regulation disturbances may be provoked or aggravated by concomitant administration of tricyclic anti-depressants or neuroleptics with alpha-receptor blocking properties.

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

Overdosage

Symptoms

Clonidine has a wide therapeutic range. The symptoms of overdosage are due to generalised sympathetic depression and include pupillary constriction, lethargy, bradycardia, hypotension, somnolence including coma, respiratory depression including apnoea. Paradoxic hypertension caused by stimulation of peripheral alpha$_1$-receptors may occur.

Treatment
Careful monitoring and symptomatic measures.

Pharmaceutical Precautions
Keep out of reach of children
Store below 25ºC

Medication Classification
Prescription Medicine

Package Quantities
Tablets, 25 mcg, 100s.

Further Information
DIXARIT® is a registered trademark.

Toxicology
Single dose toxicity studies with clonidine were performed in different animal species by oral and parenteral routes of administration. The approximate oral LD_{50} values were 70 mg/kg (mouse), 190 mg/kg (rat), > 15 mg/kg (dog), and 150 mg/kg in monkeys. Following subcutaneous injection, the LD_{50} values were > 3 mg/kg in dogs and 153 mg/kg in rats. After intravenous administration the lethal dose ranges were between 6 mg/kg (dog) and < 21 mg/kg (rat).

Toxic trans-species signs of toxicity following exposure to clonidine were exophthalmus, ataxia and tremor, independently from the route of administration. At lethal doses, tonic-clonic convulsions occurred. In addition, excitement and aggressiveness alternating with sedation (mouse, rat, dog), salivation and tachypnea (dog) as well as hypothermia and apathy (monkey) were observed.

In repeated oral dose toxicity studies up to 18 months clonidine was well tolerated at 0.1 mg/kg (rat), 0.03 mg/kg (dog) and 1.5 mg/kg (monkey). In a 13 week study in rats, the no adverse effect level (NOAEL) was 0.05 mg/kg following subcutaneous administration. After intravenous administration rabbits and dogs tolerated 0.01 mg/kg/day for 5 and 4 weeks, respectively. Higher dosages caused hyperactivity, aggression, reduced food consumption and body weight gain (rat), sedation (rabbit) or an increase in heart and liver weight accompanied by elevated serum GPT, alkaline phosphatase and alpha-globulin levels and focal liver necroses (dog).

There were no signs of any teratogenic potential after oral administration in mouse and rat at 2.0 mg/kg and rabbit at 0.09 mg/kg, or after s.c. (0.015 mg/kg, rat) and i.v. treatment (0.15 mg/kg, rabbit). In rats, increases in resorption rate were observed at oral dosage of > 0.015 mg/kg/day; however dependent on duration of dosing. Fertility in rats was not impaired up to 0.15 mg/kg. Doses up to 0.075 mg/kg did not affect the peri- and postnatal development of the progeny.

There was no mutagenic potential in the Ames test and micronucleus assay in mice. Clonidine was not tumorigenic in a carcinogenicity assay in rats.

No local irritating or sensitizing potential was found in guinea pigs and rabbits following i.v. and i.a. administrations.

Excipients
Lactose monohydrate, calcium hydrogen phosphate, maize starch dried, silica colloidal anhydrous, povidone, starch soluble, magnesium stearate, indigotindisulfonate sodium, talc, sucrose, acacia, titanium dioxide, macrogol 6000, beeswax white, carnaubawax .

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