

DISIPAL[®]

Orphenadrine hydrochloride

Presentation

DISIPAL tablets are presented as yellow sugar-coated tablets each containing 50mg orphenadrine hydrochloride, imprinted with 'I'.

Uses

Actions

Orphenadrine is an anticholinergic with a predominantly central effect and only a weak peripheral effect. In addition, it has mild antihistaminic and local anaesthetic properties.

Parkinson's syndrome is the consequence of a disturbed balance between cholinergic and dopaminergic neurotransmission in the basal ganglia caused by a decrease in dopamine.

Orphenadrine restores the physiological equilibrium and has a favourable effect on the rigidity and tremor of Parkinson's disease and Parkinsonian syndromes. The effect is somewhat less on bradykinesia.

Orphenadrine restores the motor disturbances induced by neuroleptics, in particular the hyperkinesia.

The dopamine deficiency in the striatum increases the stimulating effects of the cholinergic system.

This stimulation is counteracted by the anticholinergic effect of orphenadrine. It may have a relaxing effect on skeletal muscle spasms and it has a mood elevating effect.

Pharmacokinetics

Absorption

Orphenadrine is almost completely absorbed in the gastrointestinal tract.

Distribution

It is rapidly distributed in the tissues. Protein binding is approximately 95%.

Biotransformation

Biotransformation occurs mainly in the liver. Pharmacologically active metabolites are N-demethyl orphenadrine and N,N-didemethyl orphenadrine. After a single dose the half life value is 13-20 hours. After multiple doses this half life value may be increased.

Elimination

Within 3 days about 60% of the metabolites are excreted via the urine and about 16% with the faeces. N-demethyl orphenadrine is for 8% and N,N-didemethyl orphenadrine for 5% of the administered dose excreted in the urine. A small amount of orphenadrine (about 8%) is excreted unchanged in the urine.

Indications

Parkinson's disease, all forms of parkinsonism.

Dosage And Administration

Dosage

Parkinsonism – 150-400mg daily.

It is recommended to start with a low dose (e.g. 50mg three times daily) and to increase this slowly by 50mg every 2-3 days up to a maintenance dose of 150-250mg (maximum 400mg) daily divided into three doses, guided both by the clinical effect and the occurrence of adverse reactions.

Treatment with orphenadrine should not be discontinued abruptly and should be withdrawn gradually.

Method of Administration

DISIPAL tablets should be swallowed whole, preferably with water.

Contraindications

- Myasthenia gravis
- Prostatic hypertrophy
- Narrow angle glaucoma
- Untreated urinary retention

- Gastrointestinal obstruction
- Tardive dyskinesia
- Porphyria
- Hypersensitivity to orphenadrine or one of the other ingredients

Warnings And Precautions

- Use with caution in cases of arrhythmia or tachycardia, liver or renal function disorders and micturition disturbances.
- Acute glaucoma may occur in the case of an unknown increased eyeball pressure caused by a narrow angle of the eye chamber.
- Treatment with orphenadrine should not be stopped abruptly because this could lead to severe akinesia, agitation and/or confusion. Disturbances in water and electrolyte balance may occur due to diarrhoea and an increased sweat secretion. Elderly patients in particular develop these withdrawal symptoms. Therefore, treatment with orphenadrine should be withdrawn gradually (e.g. by reducing the dose by 50mg every 3 days).
- Elderly patients in particular are likely to incur memory and concentration disturbances and confusion. This may, erroneously, be diagnosed as dementia. It is, therefore, recommended in particular with elderly patients to start with a low dose and to increase this dose slowly, guided by the clinical effect and the occurrence of adverse reactions (see also **Dosage and Administration**).
- Orphenadrine may stimulate the occurrence of abnormal involuntary movements, in particular with the use of neuroleptics. It should not be given as prophylaxis against expected extrapyramidal adverse reactions of neuroleptics.
- If tardive dyskinesia should occur or worsen, it is advisable to discontinue treatment.
- The heat intolerance caused by decreased sweat secretion, in particular in combination with fever, may necessitate a decrease of the anticholinergic dose.
- Children in particular are very sensitive to the toxic effects of orphenadrine.
- The sodium benzoate E211 used in the sugar coat can be mildly irritating to the skin, eyes and mucous membranes.

Pregnancy and lactation

There is insufficient information available on the use of this product during pregnancy in humans to assess possibly harmful effects. There are no indications of harmful effects in animals so far. Orphenadrine passes the placenta. Based on the pharmacological action, effects on the child can be expected, as a result of which administration around parturition is dissuaded. In addition it is dissuaded to use orphenadrine during pregnancy and lactation.

Effects on ability to drive and use machines

Considering the adverse reaction profile, such as sedation, dizziness and visual disturbances, a retarded ability to react is possible. This should be taken into account when driving cars or using machines.

Adverse Effects

- Accommodation disturbances, mydriasis, dry mouth, constipation, urinary retention and heart arrhythmias. Heat intolerance to hyperthermia. Dizziness, nausea and vomiting may occur.
- Central effects: sedation, confusion, agitation, hallucinations, insomnia, euphoria, hypersensitivity, development or worsening of concentration and memory disturbances and convulsions.

Interactions

- Alcohol and chlorpromazine accelerate the metabolism of orphenadrine. Concomitant use of these agents with orphenadrine is not recommended.
- Concomitant use of other parasympatholytic medicines for Parkinsonism results in a stronger anticholinergic action and a higher risk of adverse reactions.
- Phenothiazines, amantadine, quinidine, disopyramide, tricyclic antidepressants and some antihistamines may increase anticholinergic effects of orphenadrine.

Overdosage

Hospital admission is recommended in the event of intoxication. Children are particularly sensitive to the toxic effect.

The lethal dose for adults is 2-3g (cardiotoxic).
For a child a lethal dose of 750mg has been reported.

Symptoms of intoxication

Excitation, nervousness, delirium leading to unconsciousness, tachycardia (> 100 beats per minute), convulsions, urinary retention, apnoea. Apnoea may occur 2-3 hours after intake.

Treatment of intoxication

Because stomach emptying is delayed by orphenadrine, gastric lavage and, in addition, administration of active charcoal and laxatives may also be useful some hours after ingestion. Treatment further consists of supportive therapy and maintenance of diuresis.

Routine use of physostigmine as antidote is controversial and should only be considered in extreme delirium, serious tachycardia or hypothermia.

Pharmaceutical Precautions

DISIPAL tablets can be kept at room temperature (15-25°C).

Medicine Classification

Prescription Medicine.

Package Quantities

Containers of 250 tablets.

Further Information

Preclinical safety data

No particulars.

List of excipients

Lactose, sucrose, maize starch, tribasic calcium phosphate, magnesium stearate, calcium carbonate, kaolin, talc, stearic acid, gelatin, titanium dioxide, acacia, Opaseal P-17-0200 (containing IMS, polyvinylacetate phthalate and stearic acid), Opalux yellow AS 3026 (containing sucrose, titanium dioxide, tartrazine E102, sunset yellow E110, povidone, amaranth E123 and sodium benzoate E211), Opaglos 6000 (containing ethanol, shellac, beeswax and yellow carnuba wax), and black printing ink.

Incompatibilities

Not known.

Shelf-life

DISIPAL tablets can be kept for 3 years until the expiry date printed on the package.

Name And Address

CSL Biotherapies (NZ) Ltd
666 Great South Rd
Central Park
Auckland
New Zealand

Ph: 0800 502 757

Date Of Preparation

23 July 2007

DISIPAL[®] is a registered trademark of Astellas Pharma Europe B.V.