NOVARTIS

Lioresal® 10 mg

Baclofene

Scored tablets

Composition

Active substance: 10mg of Baclofen

Excipients: Silica colloidal anhydrous, Cellulose microcrystalline, Magnesium stearate, Povidone (K 30), Wheat starch, water q.s 1 tablet

Excipient known effect: Each scored tablet contains 61mg of wheat starch.

Indications/Potential uses

Severe but reversible spasticity of the muscles resulting from multiple sclerosis.

Can be used in patients with spinal spasticity of infectious, degenerative, traumatic or neoplastic origin.

Contraindications

Known hypersensitivity to baclofen or to any of the excipients indicated under "Composition".

Warnings and precautions

Psychiatric disorders

Caution and close medical supervision are required in patients with spasticity who also suffer from psychotic disorders, schizophrenia or confusional states, as these conditions may be exacerbated by treatment with Lioresal.

Epilepsy

Particular caution is indicated in patients with epilepsy because the seizure threshold may be reduced. There have been occasional reports of seizures associated with withdrawal or overdosage of Lioresal. Appropriate anticonvulsive therapy should be continued and the patient should be closely monitored.

Other

Since adverse effects are more likely to occur in elderly patients and patients with spasticity of cerebral origin, a cautious dosage schedule should be adopted in these patients (see "Dosage/Administration").

Renal impairment

Lioresal should be used with caution in patients with renal impairment, and should not be administered to patients with end-stage renal failure unless the expected benefit of treatment outweighs the potential risk (see "Dosage/Administration").

Particular caution is required when co-administering Lioresal with medicinal products that have an adverse effect on renal function. Under such circumstances, renal function must be closely monitored and the daily dosage of Lioresal adjusted accordingly to prevent baclofen toxicity.

Hepatic impairment

No studies have been performed in patients with hepatic impairment under Lioresal therapy. The liver does not play a significant role in the metabolism of baclofen after oral administration of Lioresal (see "Pharmacokinetics"). However, Lioresal has the potential to elevate liver enzymes. Lioresal should be prescribed with caution to patients with hepatic impairment.

In addition to withdrawing treatment in patients with severe baclofen intoxication, additional haemodialysis may also be scheduled. Haemodialysis removes baclofen from the body, reduces clinical symptoms of overdosage and shortens the patient's recovery time.

Urinary retention

Neurogenic bladder may improve during treatment with Lioresal, but patients with pre-existing sphincter hypertonia may experience acute urinary retention. The product should therefore be used with caution in such patients.

Particular caution is indicated in the elderly, and in patients with severe hepatic dysfunction, acute or chronic confusional states, or disorders involving cerebral seizures.

It is primarily in the aftermath of a stroke that baclofen may be poorly tolerated, and particular caution is therefore required in stroke patients.

Caution is required when determining dosage in patients for whom spasticity is necessary for maintaining posture and locomotive ability.

Lioresal should be used with caution in patients with peptic ulcer (or a history of peptic ulcer), cerebrovascular disease, or respiratory, hepatic or renal impairment.

There have been rare reports of elevated serum levels of AST, alkaline phosphatase and glucose. Appropriate laboratory tests should therefore be performed at regular intervals in patients with liver disease or diabetes mellitus in order to ensure that no drug-induced changes have occurred in the underlying disease.

Lioresal tablets contain wheat starch, which may contain gluten, but only in trace amounts. The use of Lioresal tablets in patients with coeliac disease is therefore generally considered permissible. However, attention should be paid to possible gastrointestinal symptoms.

Postnatal convulsions have been reported after intrauterine exposure to oral Lioresal (see "Pregnancy/Breastfeeding").

Abrupt withdrawal

Avoid abrupt withdrawal of baclofen. Abrupt withdrawal or abrupt dose reduction after several months of treatment with high doses of baclofen may impair concentration and cause anxiety, confusion, delirium, visual and acoustic hallucinations, psychotic disorders, agitation, mania or paranoia, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia and - as a rebound phenomenon - temporary aggravation of spasticity.

Following abrupt withdrawal of the intrathecal formulation of Lioresal, a clinical picture has been described that resembles autonomic dysreflexia, malignant hyperthermia, neuroleptic malignant syndrome or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis.

Withdrawal of baclofen following long-term use (longer than 2 to 3 months) must be gradual, extending over the course of about 3 weeks, except in emergencies or where serious adverse effects have occurred.

Posture and balance
Lioresal should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion (see "Dosage/Administration").

Interactions

Levodopa/dopa decarboxylase (DDC) inhibitor (carbidopa)
In patients with Parkinson's disease receiving treatment with Lioresal and levodopa (alone or in combination with a DDC inhibitor, carbidopa), there have been reports of confusion, hallucinations, headaches, nausea and agitation. Worsening of the symptoms of Parkinson's disease has also been reported. Hence, caution should be exercised during concomitant administration of Lioresal and levodopa/carbidopa.

Drugs causing central nervous system (CNS) depression
Increased sedation may occur when Lioresal is taken concomitantly with other drugs causing CNS depression, including other muscle relaxants (such as tizanidine), with synthetic opiates or with alcohol (see "Effects on ability to drive and use machines" and "Warnings and precautions"). The risk of respiratory depression is also increased. In addition, hypotension has been reported with concomitant use of morphine and intrathecal baclofen. Close monitoring of respiratory and cardiovascular function is particularly important in patients with cardiopulmonary disease or weakening of the respiratory muscles.
Concomitant consumption of alcohol is particularly to be avoided since the interactions of Lioresal with alcohol are unpredictable.

Antidepressants
Concomitant administration of tricyclic antidepressants may potentiate the effect of Lioresal, resulting in pronounced muscular hypotonia.

Lithium
Concomitant use of oral Lioresal and lithium resulted in severe hyperkinetic symptoms. Caution should therefore be exercised when Lioresal is used concomitantly with lithium.

Antihypertensives
Since concomitant treatment with antihypertensives is likely to enhance the fall in blood pressure, the dosage of antihypertensive medication should be adjusted accordingly.

Agents reducing renal function
Concomitant use of medicinal products that affect renal function may reduce baclofen excretion, thereby causing toxic overdosage.

Pregnancy/Breastfeeding
Baclofen crosses the placental barrier. Reproductive toxicological effects have been observed in animal studies (see "Preclinical data"). No studies have been performed in pregnant women. The medicinal product should therefore not be used during pregnancy unless clearly necessary.

Fetotoxicity
One case of suspected withdrawal reaction (generalized convulsions) has been reported in a week-old infant whose mother had taken baclofen during pregnancy. The convulsions, which were refractory to different anticonvulsants, ceased within 30 minutes of giving baclofen to the infant. Thus far, there have not been sufficient data in humans to allow a determination of the risk to the embryo / fetus. In such a case, other possible causes (e.g. infection, electrolyte imbalances, intracranial pathologies) should be ruled out, and secondary brain damage to the infant from prolonged convulsions should be avoided.

Breastfeeding
Only small amounts of baclofen pass into the breast milk. There are no detailed data as to possible adverse effects on the infant, and the substance should therefore not be used by women who are breastfeeding.

Fertility
There are no data available on the effect of baclofen on fertility in humans. In animals, baclofen did not impair male or female fertility at non-toxic doses (see "Preclinical data").

Effects on ability to drive and use machines
During treatment with baclofen, the patient's ability to drive or to use machines may be considerably impaired. The risk is greater when alcohol is consumed during therapy. Taking into account the current dosage and the individual patient's reactions, the attending physician should therefore decide at the start of treatment whether or not the patient should be permitted to drive vehicles, use machines or perform other potentially dangerous activities.
Lioresal may cause adverse effects such as light-headedness, sedation, drowsiness, dizziness and visual impairment (see "Adverse effects"), which may impair the patient's reactions. Patients experiencing such adverse effects should be instructed not to drive or to use machines.
Special instructions should be given to patients whose working environment may place them at risk.

Overdose

Signs and symptoms
The most prominent features are signs of CNS depression: somnolence, depressed level of consciousness, coma, respiratory depression.
Also liable to occur are:
abnormal EEG (burst suppression pattern and triphasic waves), accommodation disorder, impaired pupillary reflex, generalized muscular hypotonia, myoclonus, hyporeflexia or areflexia, peripheral vasodilation, hypotension or hypertension; bradycardia or tachycardia, cardiac arrhythmias, hypothermia, nausea, vomiting, diarrhoea, salivary hypersecretion, increased hepatic enzymes (LDH, AST and ALP).
The patient's condition may deteriorate if there has been concomitant use of various centrally acting substances or drugs (e.g. alcohol, diazepam, tricyclic antidepressants).

Management
No specific antidote is known.
Intensive monitoring of the patient must begin as soon as there are any signs of baclofen overdosage. Supportive measures and symptomatic treatment are indicated

for complications such as hypotension, hypertension, convulsions, gastrointestinal disorders and respiratory or cardiovascular depression.
Owing to the risk of respiratory depression, intensive monitoring of respiratory function is indicated, with artificial respiration if necessary.
Haemodialysis should be performed in patients with severe baclofen intoxication and renal failure (see "Warnings and precautions"). Baclofen is excreted primarily via the kidneys, so sufficient fluids should be given. Forced diuresis should be used where necessary.
Physostigmine can reverse CNS effects, but should be administered with caution, as it can cause cardiac conduction disturbances, bradycardia and/or epileptic seizures.

Dosage/Administration

Treatment should be initiated with small doses of Lioresal, then gradually increased. It is recommended that the lowest effective dose be used. The optimum dosage must be individually adapted to the patient's requirements so that clonus, flexor and extensor spasms and spasticity are reduced, while avoiding adverse effects as far as possible.
In order to prevent excessive weakness and falling, Lioresal must be used with caution when spasticity is needed to maintain upright posture and balance in locomotion or other functions. It may be important to maintain a certain degree of muscle tone and allow occasional spasms to help support circulatory function and, possibly, prevent deep vein thrombosis.
Close monitoring is required at the start of treatment so that potential adverse effects such as general muscle weakness, abrupt loss of muscle tone (risk of falling!), fatigue or confusion can be rapidly detected, and the dosage adjusted as necessary.
If baclofen is to be withdrawn after prolonged administration (longer than 2–3 months), the dose should be reduced gradually over the course of about 3 weeks except in overdose-related emergencies, or where serious adverse effects have occurred (see "Warnings and precautions"), since abrupt withdrawal may occasionally be associated with anxiety and confusional states, hallucinations, cerebral seizures, dyskinesia, tachycardia or hyperthermia. Withdrawal should also be gradual on account of the risk of a transient rebound effect involving increased spasm frequency and/or severity (see "Warnings and precautions").
Treatment with Lioresal should be re-evaluated if it has not proved successful within 6–8 weeks of the patient's reaching the maximum recommended dose.

Adults

Treatment should be started with a dosage of 5 mg three times daily, given in 3 divided doses, then gradually increased. Depending on the response, each of the divided doses should subsequently be cautiously increased by 5 mg every three days. 30–80 mg per day is considered the standard daily dose, but 100 to 120 mg/day may be given in isolated cases (patients under medical supervision in hospitals).

Special dosage instructions

Children and adolescents

Experience with Lioresal tablets is limited in children and adolescents. The minimum age for treatment is 12 months.
Treatment usually starts with very low amounts, e.g. 0.3 mg/kg/day, given in 4 divided doses. The dosage should be cautiously raised, at intervals of about 1–2 weeks, until it becomes sufficient for the individual patient's requirements. The daily dosage for maintenance therapy is 0.75–2 mg/kg. However, in patients over 10 years of age, a maximum daily dose of 2.5 mg/kg may be given.
The dose should not exceed 40 mg/day in children under 8 years of age, but a maximum dose of 60 mg/day may be given in children over 8 years of age.

Elderly patients (aged 65 years or above) and patients with spasticity of cerebral origin

The dosage should be increased particularly slowly in elderly and weak patients suffering from organic brain disorders, cardiovascular disease, respiratory failure, or hepatic or renal impairment, and also in patients with spasticity of cerebral origin.

Renal impairment

Lioresal should be used with caution in patients with renal impairment. Plasma concentrations of baclofen are elevated in patients undergoing chronic haemodialysis, and a particularly low dose of Lioresal (about 5 mg/day) should therefore be selected. Signs and symptoms of overdosage have been reported with doses of over 5 mg per day in this clinical situation (see "Overdose").
Lioresal should not be used in patients with end-stage renal failure unless the expected benefit outweighs the potential risk of further treatment. Such patients must be closely monitored for early signs and symptoms of overdosage (e.g. drowsiness, lethargy; see "Warnings and precautions" and "Overdose").

Method of administration

Lioresal tablets should be taken at mealtimes with a small amount of liquid.

Adverse effects

Adverse effects occur mainly at the start of treatment (e.g. sedation, drowsiness) as well in cases in which the dosage is raised too rapidly, treatment is withdrawn abruptly following prolonged use, or large doses are employed. Adverse effects are often transient, and can be attenuated or eliminated by reducing the dosage. They are rarely severe enough to require withdrawal of therapy.
Generally speaking, adverse effects are likely to be more severe in the elderly, and in patients with cerebrovascular disturbances (e.g. stroke) or a history of psychiatric disorders.
The seizure threshold may be lowered, and seizures may occur, particularly in epileptic patients.
In isolated cases, patients showed increased muscle spasticity as a paradoxical reaction to the medicinal product.
Frequency: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), isolated cases.

Immune system disorders

Rare: Hypersensitivity reactions.