

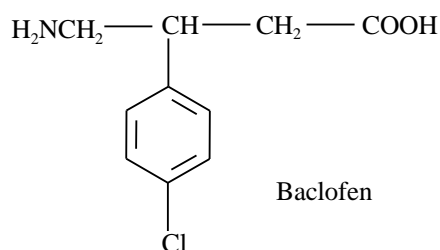
LIORESAL[®]

baclofen

NAME OF THE MEDICINE

The active ingredient of Lioresal is a gamma-aminobutyric acid derivative, baclofen, or β -(Aminomethyl)-p-chlorohydrocinnamic acid, a racemic mixture of the R(-) and S(+) isomers.

The chemical structure of baclofen is:



Empirical formula: $\text{C}_{10}\text{H}_{12}\text{ClNO}_2$

Molecular weight: 213.67

CAS number: 1134-47-0

DESCRIPTION

Baclofen is a white or almost white, odourless or practically odourless, crystalline powder. It is slightly soluble in water, very slightly soluble in methanol and insoluble in chloroform.

Lioresal tablets contain 10 mg or 25 mg baclofen. The tablets also contain the following excipients: silica-colloidal anhydrous, cellulose-microcrystalline, magnesium stearate, povidone, starch-wheat.

PHARMACOLOGY

Pharmacodynamics

Lioresal is an effective antispastic agent with a spinal site of action. Its mechanism of action and pharmacological properties are different from those of other antispastic agents.

Baclofen also has central sites of action given the adverse event profile and general CNS depressant properties.

Baclofen depresses monosynaptic and polysynaptic reflex transmission, probably by various actions, including stimulation of GABA_β-receptors. This stimulation in turn inhibits the release of excitatory amino acids (glutamate and aspartate) in guinea pig preparations. Neuromuscular transmission is not affected by baclofen.

Baclofen exerts an antinociceptive effect. The clinical significance of this awaits clarification. In neurological diseases associated with spasm of the skeletal muscles, the clinical effects of Lioresal take the form of a beneficial action on reflex muscle contractions and of marked relief from painful spasm, automatism and clonus. Lioresal, where indicated, improves the patient's mobility, making for greater independence and facilitating passive and active physiotherapy. Baclofen stimulates gastric acid secretion.

Pharmacokinetics

Absorption:

Baclofen is rapidly and completely absorbed from the gastro-intestinal tract. Maximum concentrations of unchanged drug are attained in plasma in 2 to 4 hours after an oral dose. The bioavailability of oral baclofen is 70 to 80%.

Following oral administration of a single dose of 40 mg baclofen, peak serum concentrations of 500 to 600 nanogram/mL are reached. The serum concentration remains above 200 nanogram/mL for 8 hours. The onset of action is highly variable and may range from hours to weeks.

Distribution:

The distribution volume of baclofen amounts to 0.7 litre/kg. In cerebrospinal fluid, the active substance attains concentrations approx. 8.5 times lower than in the plasma.

Baclofen is bound to plasma proteins to the extent of about 30%.

Metabolism:

About 15% of a dose of baclofen is metabolised in the liver. Deamination yields the main metabolite, β-chlorophenyl-γ-hydroxybutyric acid, which is pharmacologically inactive.

Elimination:

Approximately 70% of baclofen is eliminated in the urine in unchanged form. The plasma elimination half-life of baclofen averages 3 to 4 hours. Within 72 hours, approximately 75% of the dose is excreted via the kidneys, approximately 5% of this quantity being in the form of metabolites. The remainder of the dose, including 5% as metabolites, is excreted in the faeces.

INDICATIONS

Suppression of voluntary muscle spasm in:

- Multiple sclerosis

- Spinal lesions of traumatic, infectious, degenerative, neoplastic and unknown origin, causing:
 - skeletal hypertonus
 - spastic and dyssynergic bladder dysfunction

Not recommended in Parkinson's disease or spasticity arising from strokes, cerebral palsy or rheumatoid disorders.

CONTRAINDICATIONS

Known hypersensitivity to baclofen or to any of the components of the formulation.

PRECAUTIONS

Psychiatric and nervous system disorders

Patients suffering not only from spasticity but also from psychotic disorders, schizophrenia, depressive or manic disorders or confusional states should be treated cautiously with Lioresal and kept under careful surveillance, because exacerbations of these conditions may occur.

Epilepsy or other potential convulsive conditions

Caution is needed in patients with epilepsy or other convulsive conditions, cortical or subcortical brain damage or significant EEG abnormalities, since ingestion of baclofen may cause deterioration of seizure control and EEG changes and may precipitate convulsions. In patients with epilepsy and muscle spasticity, Lioresal can be employed under appropriate supervision, provided adequate anticonvulsive therapy is continued.

Lowering of the convulsion threshold may occur and seizures have been reported occasionally after cessation of Lioresal or with overdosage.

Others

Lioresal should be used with caution in patients with:

- peptic ulcers or with a history of peptic ulcers
- cerebrovascular diseases or from respiratory or hepatic insufficiency.
- porphyria
- a history of alcoholism
- diabetes mellitus (baclofen may increase blood glucose concentrations)
- hypertension (see "INTERACTIONS WITH OTHER MEDICINES")

Since unwanted effects are more likely to occur, a cautious dosage schedule should be adopted in elderly and patients with spasticity. Lioresal is not recommended in Parkinson's disease or spasticity arising from strokes, cerebral palsy or rheumatoid disorders.

Changes in muscle tone

Lioresal should be used with caution in patients who use spasticity to maintain upright posture and balance in moving. If an undesirable degree of muscular hypotonia occurs, making it more difficult for patients to walk or fend for themselves, this can usually be relieved by adjusting the dosage (i.e. by reducing the doses given during the day and possibly increasing the evening dose).

During treatment with Lioresal, neurogenic disturbances affecting the emptying of the bladder may improve, whereas in patients with pre-existing sphincter hypertonia, acute retention of urine may occur. The drug should, therefore, be used with caution in such cases.

Hepatic impairment

Because baclofen is partially metabolised in the liver, patients with impaired liver function should be periodically monitored with laboratory tests (see “DOSAGE AND ADMINISTRATION - Monitoring Advice”).

Renal impairment

Since baclofen is largely eliminated by the kidneys, a dosage reduction is advised to avoid drug accumulation. Lioresal should be used with caution in patients with renal impairment and should be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk (see “DOSAGE AND ADMINISTRATION - Renal impairment”).

Neurological signs and symptoms of overdose including clinical manifestations of toxic encephalopathy (e.g. confusion, somnolence, hallucination) have been observed in patients with renal impairment taking Lioresal at doses at and above 5 mg daily. Patients with renal impairment should be closely monitored for prompt diagnosis of early signs and symptoms of toxicity (see “OVERDOSAGE”).

Particular caution is required when combining Lioresal to drugs or medicinal products that can significantly impact renal function. Renal function shall be closely monitored and Lioresal daily dosage adjusted accordingly to prevent baclofen toxicity.

Besides discontinuing treatment, unscheduled haemodialysis might be considered as a treatment alternative in patients with severe baclofen toxicity. Haemodialysis effectively removes baclofen from the body, alleviates clinical symptoms of overdose and shortens the recovery time in these patients.

Abrupt discontinuation

Anxiety and confusional states, delirium, hallucinations, psychotic disorders, mania, or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia and - as a

rebound phenomenon - temporary aggravation of spasticity have been reported upon the abrupt withdrawal of Lioresal, especially after long-term medication.

Drug withdrawal reactions including postnatal convulsions in neonates have been reported after intrauterine exposure to oral Lioresal. (See “Use in Pregnancy”).

For the intrathecal formulation of Lioresal, it has been reported that clinical characteristics of withdrawal may resemble autonomic dysreflexia, infection (sepsis), malignant hyperthermia, neuroleptic-malignant syndrome, or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis.

Except in overdose-related emergencies or where serious adverse effects have occurred, treatment should, therefore, always be gradually withdrawn by successive dosage reduction over a period of approximately 1 to 2 weeks.

If withdrawal symptoms occur, restarting baclofen therapy and withdrawing over a longer period may help to resolve withdrawal problems.

Switching from oral to intrathecal baclofen and vice versa

An attempt should be made to discontinue concomitant antispastic medication to avoid possible overdose or adverse drug interactions. This should preferably be done before switching from oral to intrathecal baclofen or vice versa and requires careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispastics during chronic therapy with baclofen should be avoided.

Effect on ability to drive or use machinery

Lioresal may be associated with adverse effects such as dizziness, sedation, somnolence and visual impairment (see “ADVERSE EFFECTS”) which may impair the patient’s reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines.

The patient's ability to react may be adversely affected by sedation and decreased alertness caused by Lioresal. Patients should, therefore, exercise due caution when driving a vehicle or operating machinery.

Posture and balance

Lioresal should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion (see “DOSAGE AND ADMINISTRATION”).

Wheat starch

Lioresal tablets contain wheat starch. Wheat starch may contain gluten, but only in trace amounts.

Effects on Fertility

There are no data available on the effect of baclofen on fertility in humans.

Use in Pregnancy (Category B3)

Risk summary

There are no adequate and well-controlled studies in pregnant women. Animal data showed that baclofen crosses the placental barrier. Therefore, Lioresal should not be used during pregnancy unless the expected benefit outweighs the potential risk to the foetus.

Drug withdrawal reactions including postnatal convulsions in neonates following intra-uterine exposure to oral baclofen, have been reported. In one suspected case of postnatal baclofen withdrawal, the convulsions were refractory to various anticonvulsants, but responsive to the administration of baclofen to the affected neonate (See "PRECAUTIONS, Abrupt discontinuation").

Animal data

In two teratogenic studies in pregnant rats, baclofen has been shown to increase the incidence of omphaloceles (ventral hernias) in fetuses at a dose of 20 mg/kg/day, which is maternotoxic. The relevance of this finding to humans is unknown. At the same dose there was also an increased incidence of incomplete sternebral ossification in the fetuses.

In mice, no teratogenic effects were observed at a dose of 81.5 mg/kg/day given via the diet or up to 40 mg/kg/day given by gavage. At 40 mg/kg/day by gavage, a delay in fetal growth was associated with maternal anorexia. The lack of maternotoxicity seen in the dietary study suggests that the dose used was inadequate.

In pregnant rabbits, oral doses up to 10 mg/kg/day were manifested as a sedative effect. Skeletal examination of fetuses revealed a marked increase in the absence of ossification of the phalangeal nuclei of fore-limbs and hind-limbs.

Use in Lactation

Studies in lactating women are limited to one (1) patient. In this particular case, available evidence suggests that baclofen is found in quantities so small that adverse effects in the infant would have been unlikely.

Genotoxicity

Baclofen did not induce mutations in bacterial or mammalian cells in vitro, lacked DNA damaging activity in the sister chromatid exchange assay and had no clastogenic activity in the nuclear anomaly test.

Carcinogenicity

A two year carcinogenicity study in rats found no evidence that baclofen had carcinogenic potential at oral doses up to 100 mg/kg/day. An apparently dose-related increase in the incidence of ovarian cysts and enlarged and/or haemorrhagic adrenals at the highest two doses (50 and 100 mg/kg/day) was observed in female rats. The clinical relevance of these findings is not known.

Ovarian cysts have been found by palpation in about 5% of the multiple sclerosis patients who were treated with oral Lioresal for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are known to occur spontaneously in a proportion of the normal female population.

INTERACTIONS WITH OTHER MEDICINES

Levodopa/Dopa Decarboxylase (DDC) inhibitor (Carbidopa):

In patients with Parkinson's disease receiving treatment with Lioresal and levodopa (alone or in combination with DDC inhibitor, carbidopa), there have been reports of mental confusion, hallucinations, headaches, nausea and agitation. Worsening of the symptoms of Parkinsonism 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 "PRECAUTIONS"). The risk of respiratory depression is also increased. In addition, hypotension has been reported with concomitant use of morphine and intrathecal baclofen. Careful monitoring of respiratory and cardiovascular functions is essential, especially in patients with cardiopulmonary disease and respiratory muscle weakness.

Antidepressants:

During concomitant treatment with tricyclic antidepressants, the effect of Lioresal may be potentiated, resulting in pronounced muscular hypotonia.

Lithium:

Concurrent use of oral Lioresal and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should 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:

Drugs or medicinal products that can significantly impact renal function may reduce baclofen excretion leading to toxic effects (see “PRECAUTIONS, Impaired renal function”).

Others:

Concurrent use of baclofen with monoamine oxidase (MAO) inhibitors may result in increased CNS-depressant and hypotensive effects. Caution is recommended and dosage of one or both agents may require reduction.

Since baclofen may increase blood glucose concentrations, dosage adjustments of insulin and/or oral hypoglycaemic agents may be necessary during and after concurrent therapy.

Studies in rats indicate that the agonistic effects of baclofen on gastric acid secretion are potentiated by diazepam.

ADVERSE EFFECTS

Adverse effects occur mainly at the start of treatment (e.g. sedation, somnolence), if the dosage is increased too rapidly, if large doses are employed or if the patient is elderly. They are often transitory and can be attenuated or eliminated by reducing the dosage. They may necessitate withdrawal of the medication. In patients with a history of psychiatric illness, cortical or organic brain disorders or with cerebrovascular disorders (eg. stroke), as well as in elderly patients, adverse reactions may be more serious.

It is often difficult to distinguish whether some of these are drug effects or manifestations of the diseases under treatment. Psychiatric manifestations can occur in acute or chronic toxicity due to baclofen.

Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients (see “PRECAUTIONS”).

Certain patients have shown increased muscle spasticity as a paradoxical reaction to the medication.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$) very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Nervous system disorders

Very common: Sedation, somnolence

Common: Respiratory depression, fatigue, confusional state, dizziness, personality changes, vertigo, headache, insomnia, euphoric mood, depression, muscular weakness, ataxia, tremor, hallucination, nightmare, myalgia,

nystagmus, dry mouth, tinnitus
 Rare: Paraesthesia, dysarthria, dysgeusia, syncope, dyskinesia, coma, taste disturbances
 Very rare: Hypothermia

Eye disorders

Common: Accommodation disorder, visual impairment

Cardiac disorders

Common: Cardiac output decreased
 Rare: Arrhythmias, palpitations, chest pain
 Not known: Bradycardia

Vascular disorders

Common: Hypotension
 Rare: Dyspnoea, ankle oedema

Gastrointestinal disorders

Very common: Nausea (particularly at the start of treatment)
 Common: Gastrointestinal disorder, retching, vomiting, constipation, diarrhoea
 Rare: Colicky abdominal pain, anorexia

Hepatobiliary disorders

Rare: Hepatic function abnormal

Skin and subcutaneous tissue disorders

Common: Hyperhidrosis, rash, pruritus
 Not known: Urticaria

Renal and urinary disorders

Common: Pollakiuria, enuresis, dysuria
 Rare: Urinary retention, nocturia, haematuria

Reproductive system and breast disorders

Rare: Erectile dysfunction, inability to ejaculate

General disorders and administration site conditions

Very rare: Hypothermia
 Not known: Drug withdrawal syndrome*

Investigations

Not known: Blood glucose increase

Miscellaneous

Rare: nasal congestion, weight gain

*Drug withdrawal syndrome including postnatal convulsions has also been reported after intra-uterine exposure to oral Lioresal

DOSAGE AND ADMINISTRATION

Treatment with Lioresal should always be started in hospital, using small doses which are then gradually increased in a stepwise manner. The lowest dose compatible with an optimal response is recommended. The optimum daily dosage should be individualised so that clonus, flexor and extensor spasms, and spasticity are reduced, at the same time retaining enough muscle tone to permit active movements and avoiding adverse effects as far as possible.

In order to prevent excessive weakness and falling, Lioresal should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion or whenever spasticity is used to maintain function. It may be important to maintain some degree of muscle tone and allow occasional spasms to help support circulatory function.

Abrupt discontinuation of treatment should be avoided (see "PRECAUTIONS").

In adults Lioresal should be given in at least three divided doses daily.

Dosage Regimen

As a rule, treatment should be started with a dose of 5 mg three times daily, subsequently increased at 3-day intervals by 5 mg three times daily (i.e. the dosage regimen is 5 mg three times a day for 3 days, then 10 mg three times a day for 3 days, etc.) until the optimum response has been attained. In certain patients reacting sensitively to drugs, it may be advisable to begin with a lower daily dose (5 mg or 10 mg), increased by smaller steps at longer intervals (see "PRECAUTIONS"). The optimum dosage generally ranges from 30 mg to 75 mg daily, although occasionally in hospitalised patients daily doses up to 100 mg may be necessary.

If no benefit is apparent within 6 to 8 weeks of achieving the maximum dosage, a decision should be taken whether or not to continue treatment with Lioresal.

Discontinuation of the treatment should always be gradual by successively reducing the dosage over a period of approximately 1 to 2 weeks, except in overdose-related emergencies, or where serious adverse effects have occurred (see "PRECAUTIONS").

Special Populations

Renal impairment:

In patients with impaired renal function or undergoing chronic haemodialysis, low doses (ie. approx. 5 mg daily) should be used. These patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy) (see “PRECAUTIONS” and “OVERDOSAGE”). Signs and symptoms of overdosage have been reported with doses at and above 5 mg daily in this setting (see “OVERDOSAGE”).

Lioresal should be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk.

Hepatic impairment:

No studies have been performed in patients with hepatic impairment under Lioresal therapy. Lioresal should be prescribed with caution in patients with hepatic impairment (see “PRECAUTIONS”).

Elderly patients (aged 65 years or above):

Since unwanted effects are more likely to occur in elderly patients (due to increased risk of renal function impairment and CNS toxicity), a very cautious dosage schedule should be adopted and the patient kept under appropriate surveillance.

Toxicity due to baclofen may be mistaken for uraemic encephalopathy.

Paediatric patients:

Lioresal should be given with extreme caution to children under 16 years of age, as only limited data are available. Lioresal tablets are not suitable for use in children with a body weight below 33 kg.

Method of administration

Lioresal should be taken during meals with a little liquid.

Monitoring Advice

Since in rare instances elevated AST, alkaline phosphatase or glucose levels in the serum have been recorded, appropriate laboratory tests should be performed periodically in patients with liver diseases or diabetes mellitus, in order to ensure that no drug-induced changes in these underlying diseases have occurred.

Careful monitoring of respiratory and cardiovascular function is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

OVERDOSAGE

Signs and symptoms

Prominent features are signs of central nervous depression: somnolence, depressed level of consciousness, respiratory depression due to absent respiratory movement, coma.

Also liable to occur are: confusion, hallucinations, agitation, abnormal electroencephalogram (burst suppression pattern and triphasic waves), accommodation disorders, impaired pupillary reflex; generalised muscular hypotonia, myoclonus, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension or hypertension, bradycardia, tachycardia or cardiac arrhythmias, hypothermia, nausea, vomiting, diarrhoea, salivary hypersecretion; increased hepatic enzymes, sleep apnoea, rhabdomyolysis.

A deterioration in the condition may occur if various substances or drugs acting on the central nervous system (e.g. alcohol, diazepam, tricyclic antidepressants) have been taken at the same time.

Adult patients have ingested up to 1125 mg of baclofen and survived. Ingestion of 1250 to 2500 mg by one patient was fatal. Serious poisoning has occurred with doses of 150 and 300 mg in adults.

Treatment

No specific antidote is known.

Supportive measures and symptomatic treatment should be given for complications such as hypotension, hypertension, convulsions, gastrointestinal disturbances, and respiratory or cardiovascular depression.

Symptomatic treatment should include the following:

- elimination of the drug from the gastrointestinal tract e.g. administration of activated charcoal; if necessary, saline laxatives
- since the drug is excreted chiefly via the kidneys, generous quantities of fluid should be given, possibly together with a diuretic.
- measures in support of cardiovascular functions
- in the case of respiratory muscle weakness, administration of artificial respiration
- in the event of convulsions, diazepam should be administered cautiously i.v., paying attention to increased muscle relaxation and possible respiratory insufficiency, if the patient is not already being artificially ventilated.
- Haemodialysis (some times unscheduled) may be useful in severe poisoning associated with renal failure (see PRECAUTIONS)

Contact the Poisons Information Centre on 13 11 26 for advice on management.

PRESENTATION AND STORAGE CONDITIONS

Tablets containing baclofen 10mg: white, round, flat with bevelled edges; marked with KJ and score, CG on reverse. Bottles of 100.

Tablets containing baclofen 25mg: white, round, flat with bevelled edges; marked with UR and score, CG on reverse. Bottles of 100 and blister packs of 50 and 100.

Storage: Store below 25°C. Medicines should be kept out of the reach of children.

NAME AND ADDRESS OF THE SPONSOR

NOVARTIS Pharmaceuticals Australia Pty Limited
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POISON SCHEDULE OF THE MEDICINE

Poison schedule: 4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 August 2001

DATE OF MOST RECENT AMENDMENT

1 November 2017

Internal document code:

lrst011117i based on the CDS dated 17 August 2017