Lioresal®

Antispastic with spinal site of action

DESCRIPTION AND COMPOSITION

Pharmaceutical forms

Lioresal scored tablets: 10 mg of baclofen.

White to faintly yellowish, round, flat tablets with a slightly bevelled edge. Debossed with "CG" on one side and the other the debossment "K", score "J". The score line on one side is to divide the tablet into equal doses.

Active substance

Baclofen

EXCIPIENTS

Tablets: wheat starch; cellulose microcrystalline; povidone; silica colloidal anhydrous; magnesium stearate.

Pharmaceutical formulations may vary between countries.

INDICATIONS

Adult and Paediatric population (6-<18 years)

Lioresal is indicated for the symptomatic treatment of spasticity of cerebral origin, especially where due to infantile cerebral palsy, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

Lioresal is also indicated for the symptomatic treatment of muscle spasms occurring in spinal cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin such as multiple sclerosis, spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

DOSAGE REGIMEN AND ADMINISTRATION

Dosage regimen

Treatment should always be initiated with small, gradually increasing doses of Lioresal. The lowest dose compatible with an optimal response is recommended. The optimum daily dosage should be adapted to each individual in such a way that clonus, flexor and extensor spasms and spasticity are reduced, but adverse effects are avoided as far as possible.

If no benefit is apparent within 6 to 8 weeks of achieving the maximum dosage, a decision should be made whether to continue using Lioresal.

Discontinuation of 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 section WARNINGS AND PRECAUTIONS).

Adults

Treatment should be started with a dosage of 15 mg daily, preferably in 3 divided doses. The dose should be titrated upwards cautiously by 15 mg/day increments at 3-day intervals until the requisite daily dosage has been attained. In certain patients reacting sensitively to drugs, it may be advisable to begin with a lower daily dosage (5 or 10 mg) and to raise this dosage more gradually (see section WARNINGS AND PRECAUTIONS). The optimum dosage generally ranges from 30 to 75 mg daily. Daily doses of 100 to 120 mg may be given to carefully monitored patients in hospital.

Special populations

Pediatric patients (6-<18 years)

Treatment should usually be started with a very low dose (corresponding to approximately 0.3mg/kg a day), preferably in 4 divided doses. Therefore, Lioresal tablets are not suitable for use in children with a body weight below 33 kg.

The dosage should be cautiously increased, at about 3-day intervals, until it becomes sufficient for the child's individual requirements.

The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight. The total daily dose should not exceed a maximum of 40 mg/day in children below 8 years of age. In children over 8 years of age a maximum daily dose of 60 mg/day may be given.

The recommended daily dosages for maintenance therapy are as follows:

Children aged 6 years – 8 years: 30 – 40mg

Over 8 years: up to 60mg

Renal impairment

In patients with impaired renal function**,** Lioresal should be given with caution and at lower doses. These patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy) (see section WARNINGS AND PRECAUTIONS and section OVERDOSAGE).

In patients undergoing chronic hemodialysis, baclofen concentrations in plasma are elevated and therefore a particularly low dosage of Lioresal should be selected, i.e. approx. 5 mg daily (see section WARNINGS AND PRECAUTIONS).

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 on Lioresal therapy. The liver does not play a significant role in the metabolism of baclofen after oral administration of Lioresal (see section CLINICAL PHARMACOLOGY). However, Lioresal has the potential of

elevating liver enzymes. Lioresal should be prescribed with caution in patients with hepatic impairment (see section WARNINGS AND PRECAUTIONS).

Geriatric patients (aged 65 years or above)

Since adverse effects are more likely to occur in **elderly patients**, it is recommended that a cautious dosage schedule be adopted in such cases and that the patient be kept under appropriate surveillance.

Patients with spastic states of cerebral origin

Since adverse effects are more likely to occur in patients with spastic states of cerebral origin, it is recommended that a cautious dosage schedule be adopted in such cases and that the patient be kept under appropriate surveillance.

Method of administration

Lioresal should be taken during meals with a little liquid.

CONTRAINDICATIONS

Known hypersensitivity to baclofen or to any of the excipients.

WARNINGS AND PRECAUTIONS

Psychiatric and nervous system disorders

Patients suffering from psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson's disease, should be treated cautiously with Lioresal and kept under careful surveillance, because these conditions may become exacerbated.

Suicide and suicide-related events have been reported in patients treated with baclofen. In most cases, the patients had additional risk factors associated with an increased risk of suicide including alcohol use disorder, depression and/or a history of previous suicide attempts. Close supervision of patients with additional risk factors for suicide should accompany therapy with Lioresal. Patients (and caregivers of patients) should be alerted about the need to monitor for clinical worsening, suicidal behavior or thoughts or unusual changes in behavior and to seek medical advice immediately if these symptoms present.

Epilepsy

Special attention should be given to patients known to suffer from epilepsy since lowering of the convulsion threshold may occur and seizures have occasionally been reported in connection with the discontinuation of Lioresal or with overdosage. Adequate anticonvulsive therapy should be continued and the patient should be carefully monitored.

Others

Lioresal should be used with caution in patients with, or with a history of, peptic ulcers, as well as in patients with cerebrovascular diseases or with respiratory, hepatic, or renal insufficiency.

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.

Since adverse effects are more likely to occur, a cautious dosage schedule should be adopted in elderly and patients with spasticity of cerebral origin (see section DOSAGE REGIMEN AND ADMINISTRATION).

Renal impairment

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 section DOSAGE REGIMEN AND ADMINISTRATION).

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 of more than 5mg per day. Patients with renal impairment should be closely monitored for prompt diagnosis of early signs and symptoms of toxicity (see section OVERDOSAGE).

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

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

Urinary disorders

On Lioresal treatment, neurogenic disturbances affecting the emptying of the bladder may show an improvement. In patients with pre-existing sphincter hypertonia, acute retention of urine may occur; the drug should be used with caution in such cases.

Laboratory tests

In rare instances, elevated aspartate aminotransferase, blood alkaline phosphatase and blood glucose levels in the serum have been recorded. Appropriate laboratory tests should therefore be performed periodically in patients with liver disease or diabetes mellitus in order to ensure that no drug-induced changes in these underlying diseases have occurred.

Abrupt discontinuation

Anxiety and confusional state, delirium, hallucination, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and - as a rebound phenomenon - temporary aggravation of spasticity and hypertonia have been reported following 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 section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

For the intrathecal formulation of Lioresal, it has been reported that clinical characteristics of withdrawal may resemble autonomic dysreflexia, 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, the treatment should always be gradually discontinued by successively reducing the dosage (over a period of approximately 1 to 2 weeks).

Driving and using machines

Lioresal may be associated with adverse effects such as dizziness, sedation, somnolence and visual impairment (see Section ADVERSE DRUG REACTIONS) which may negatively affect the patient's reaction times. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines.

Posture and balance

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

INTERACTIONS

Observed interactions to be considered

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 co-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 Driving and using machines under section 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. 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

Concomitant use of oral Lioresal and lithium resulted in aggravated hyperkinetic symptoms. Thus, caution should be exercised when Lioresal is used concomitantly with lithium.

Antihypertensives and other drugs known to lower blood pressure

Since concomitant treatment with drugs that lower blood pressure is likely to increase the fall in blood pressure, the dosage of concomitant medications 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 section WARNINGS AND PRECAUTIONS).

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

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 fetus.

Clinical considerations

Fetal/Neonatal adverse reactions

Drug withdrawal reactions including postnatal convulsions in neonates have been reported after intra-uterine exposure to oral Lioresal (see section WARNINGS AND PRECAUTIONS).

Animal data

Oral baclofen was shown to not have adverse effects on fertility or postnatal development at non-maternally toxic dose levels in rats. Baclofen is not teratogenic in mice, rats, and rabbits at doses at least 2.1-times the maximum oral mg/kg dose in adults. Baclofen given orally has been shown to increase the incidence of omphaloceles (ventral hernias) in rat fetuses given approximately 8.3-times the maximum oral adult dose expressed as a mg/kg dose. This abnormality was not seen in mice or rabbits. Baclofen dosed orally has been shown to cause delayed fetal growth (ossification of bones) at doses that also caused maternal toxicity in rats and rabbits.

LACTATION

In mothers taking Lioresal at therapeutic doses, the active substance passes into the breast milk, but in quantities so small that no adverse effects are to be expected in the infant.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Infertility

There is no data available on the effect of baclofen on human fertility. Baclofen did not impair male or female fertility in rats at dose levels not toxic to them.

ADVERSE DRUG REACTIONS

Adverse effects occur mainly at the start of treatment (e.g. sedation, somnolence), if the dose is increased too rapidly, or if large doses are used. They are often transitory and can be attenuated or eliminated by reducing the dosage; they are rarely severe enough to require stopping the medication. In patients with a history of psychiatric illness or with cerebrovascular disorders (e.g. stroke), as well as in elderly patients, adverse reactions may be more serious.

Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients.

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

Many of the side effects reported are known to occur in association with the underlying conditions being treated.

Adverse drug reactions (Table 1) are listed according to system organ class in MedDRA. Within each system organ class, adverse reactions are ranked by frequency, with the most frequent reactions first, using the following convention (CIOMS III): very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are raked in order of decreasing seriousness.

Table 1 Tabulated summary of adverse drug reactions

Immune system disorders	
Not known:	Hypersensitivity
Psychiatric disorders	
Common:	Confusional state, hallucination, depression, insomnia, euphoric mood, nightmare
Nervous system disorders	
Very common:	Sedation, somnolence.
Common:	Dizziness, headache, ataxia, tremor, nystagmus, .
Rare:	Paraesthesia, dysarthria, dysgeusia.
Eye disorders	
Common:	Accommodation disorders, visual impairment.
Cardiac disorders	
Common:	Cardiac output decreased.
Not known:	Bradycardia
Vascular disorders	
Common:	Hypotension.
Gastrointestinal disorders	
Very common:	Nausea.
Common:	Gastrointestinal disorder, retching, vomiting, dry mouth, constipation, diarrhoea.
Rare:	Abdominal pain.
Hepatobiliary disorders	
Rare:	Hepatic function abnormal.
Skin and subcutaneous tissue disorders	
Common:	Hyperhidrosis, rash.

Not known:	Urticaria, alopecia
Musculoskeletal and connective tissue disorders	
Common:	Muscle weakness, myalgia
Renal and urinary disorders	
Common:	Pollakiuria, enuresis, dysuria.
Rare:	Urinary retention.
Reproductive system and breast disorders	
Rare:	Erectile dysfunction.
Not known:	Sexual dysfunction
Respiratory, thoracic and mediastinal disorders	
Common	Respiratory depression
General disorders and administration site conditions	
Common:	Fatigue
Very rare:	Hypothermia
Not known:	Drug withdrawal syndrome (see section WARNINGS AND PRECAUTIONS), swelling face and peripheral oedema
Investigations	
Not known:	Blood glucose increased

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

OVERDOSAGE

Signs and symptoms

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

The following symptoms may also occur: confusion hallucination, agitation, convulsion, abnormal electroencephalogram (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 or cardiac arrhythmia, hypothermia, nausea, vomiting, diarrhea, salivary hypersecretion, increased hepatic enzymes, sleep apnea, rhabdomyolysis, tinnitus.

A deterioration of the overdose syndrome 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.

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.

Since the drug is excreted chiefly via the kidneys, generous quantities of fluid should be given, possibly together with a diuretic. Hemodialysis (sometimes unscheduled) may be useful in cases of severe poisoning associated with renal failure (see section WARNINGS AND PRECAUTIONS).

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

Lioresal is a highly effective antispastic with a spinal site of action. Baclofen depresses monosynaptic and polysynaptic reflex transmission in the spinal cord by stimulating the $GABA_B$-receptors, this stimulation in turn inhibiting the release of the excitatory amino acids glutamate and aspartate.

Pharmacodynamics

Neuromuscular transmission is not affected by baclofen. Baclofen has an antinociceptive effect. In neurological diseases associated with skeletal muscles spasms, the clinical effects of Lioresal take the form of a beneficial action on reflex muscle contractions and marked relief from painful spasm, automatism, and clonus. Lioresal improves the patient's mobility, making it easier to carry out daily activities (including catheterization) and physiotherapy.

Baclofen stimulates gastric acid secretion.

Pharmacokinetics

Absorption

Baclofen is rapidly and completely absorbed from the gastrointestinal tract.

No significant difference between syrup and tablet formulation is observed in respect of T_{max}, C_{max}, and bioavailability.

Following oral administration of single doses of 10, 20, and 30 mg baclofen, peak plasma concentrations averaging about 180, 340, and 650 naonogram/mL, respectively, are recorded after 0.5 to 1.5 hours. The corresponding areas under the serum concentration curves (AUCs) are proportional to the size of the dose.

Distribution

The distribution volume of baclofen amounts to 0.7 L/kg. The protein binding is approximately 30% and is constant in the concentration range of 10 nanogram/mL to 300 microgram/mL. In the cerebrospinal fluid, the active substance attains concentrations approx. 8.5 times lower than in the plasma.

Biotransformation

Baclofen is metabolized to only a minor extent. Deamination yields the main metabolite, beta-(p-chlorophenyl)-4-hydroxybutyric acid, which is pharmacologically inactive.

Elimination/Excretion

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

Special populations

Geriatric patients (aged 65 years of age or above)

The pharmacokinetics of baclofen in elderly patients are virtually the same as in patients below 65 years of age. Following a single oral dose, elderly patients have slower elimination but a similar systemic exposure of baclofen compared to adults below 65 years of age. Extrapolation of these results to multi-dose treatment suggests no significant pharmacokinetic difference between patients below 65 years of age and elderly patients.

Pediatric patients

Following oral administration of the 2.5 mg Lioresal tablet in children (aged 2 to12 years), C_{max} of 62.8±28.7 nanogram/mL, and T_{max} in the range of 0.95 to 2 hours have been reported. Mean plasma clearance (Cl) of 315.9 mL/h/kg; volume of distribution (Vd) of 2.58 L/kg; and half-life ($T_{1/2}$) of 5.10 hours have been reported.

Hepatic impairment

No pharmacokinetic data is available in patients with hepatic impairment after administration of Lioresal. However, as the liver does not play a significant role in the disposition of baclofen, it is unlikely that baclofen pharmacokinetics would be altered to a clinically significant level in patients with hepatic impairment.

Renal impairment

No controlled clinical pharmacokinetic study is available in patients with renal impairment after administration of Lioresal. Baclofen is predominantly eliminated unchanged in the urine. Sparse plasma concentration data collected only in female patients under chronic hemodialysis or compensated renal failure indicate significantly decreased clearance and increased half-life of baclofen in these patients. Dosage adjustment of baclofen based on its systemic levels should be considered in patients with renal impairment, and prompt hemodialysis is an effective means of reversing excess baclofen in systemic circulation.

CLINICAL STUDIES

No recent clinical trials have been conducted with Lioresal.

NON-PRECLINICAL SAFETY DATA

Reproductive toxicity

For reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Mutagenicity and Carcinogenicity

Baclofen did not show any mutagenic and genotoxic potential in tests in bacteria, mammalian cells, yeast, and Chinese hamsters. The evidence suggests that baclofen is unlikely to have mutagenic potential.

Baclofen showed no carcinogenic potential in a 2-year study in rats. An apparently dose-related increase in the incidence of ovarian cysts and of enlarged and/or haemorrhagic adrenals at the maximum dose used (50 to 100 mg/kg) were observed in female rats treated with baclofen for two years.

INCOMPATIBILITIES

None known.

STORAGE

See folding box.

Lioresal should not be used after the date marked “EXP” on the pack.

Lioresal must be kept out of the sight and reach of children.

INSTRUCTIONS FOR USE AND HANDLING

There are no specific instructions for use and handling.

Manufacturer:

See folding box.

® = registered trademark

Novartis Pharma AG, Basel, Switzerland