LIORESAL®

Antispastic with spinal site of attack; gamma-aminobutytric acid (GABA) derivatives.

Description and composition

Pharmaceutical forms

Tablet

Active substance

Baclofen

Excipients

Aerosil 200 – Colloidal silicon dioxide, magnesium stearate, polyvinylpyrollidone, microcrystalline cellulose (Avicel PH101, Avicel PH 102), corn starch, purified water.

Indications

Adults

Treatment of spasticity of the skeletal muscles in multiple sclerosis.

Treatment of spastic conditions occur in spinal-cord diseases of infections, degenerative, traumatic, neoplastic, or unknown origin: e.g. spastic spinal paralysis, amyotrophic lateral sclerosis, syringo-myelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord; muscle spasm 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.

Dosage regimen and administration

Dosage regimen

Before starting treatment with Lioresal it is prudent to realistically assess the overall extent of clinical improvement that the patient may be expected to achieve. Careful titration of dosage is essential (particularly in the elderly) until the patient is stabilized. If too high a dose is initiated or if the dosage is increased too rapidly side effects may occur. This is particularly relevant if the patients is ambulant in order to minimize muscle weakness in the unaffected limbs or where spasticity is necessary for support.

Adults

The following gradually increasing dosage regimen is suggested, but should be adjusted to suit individual patient requirements.

5 mg three times a day for three days
10 mg three times a day for three days
15 mg three times a day for three days
20 mg three times a day for three days

Satisfactory control of symptoms is usually obtained with doses of up to 60 mg daily, but a careful adjustment is often necessary to meet the requirements of each individual patient. The dose may be increased slowly if required, but a maximum daily dose of more than 100 mg is not advised unless the patient is in hospital under careful medical supervision. Small frequent dosage may prove better in some cases than larger spaced doses. Also some patients benefit from the use of Lioresal only at night to counteract painful flexor spasm. Similarly a single dose given approximately 1 hour prior to

performance of specific tasks such as washing, dressing, shaving, physiotherapy, will often improve mobility.

Once the maximum recommended dose has been reached, if the therapeutic effect is not apparent within 6 weeks a decision whether to continue with Lioresal should be taken.

Special populations

Geriatric patients (aged 65 years or above)

Elderly patients may be more susceptible to side effects, particularly in the early stages of introducing Lioresal. Small doses should therefore be used at the start of treatment, the dose being titrated gradually against the response, under careful supervision. There is no evidence that the eventual average maximum dose differs from that in younger patients.

Renal impairment

In patients with impaired renal function or undergoing chronic haemodialysis, a particularly low dosage of Lioresal should be selected i.e. approx. 5 mg daily. 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).

Signs of overdose have been observed in patients with renal impairment taking oral Lioresal at doses of more than 5 mg per day.

Lioresal should only be administered to end stage renal failure patients when benefit outweighs risk.

Hepatic impairment

No studies have been performed in patients with hepatic impairment under Lioresal therapy. Liver does not play 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).

Patients with spastic states of cerebral origin

Unwanted effects are more likely to occur in these patients. It is therefore recommended that a very cautious dosage schedule be adopted and that patients be kept under appropriate surveillance.

Method of administration

Lioresal should be taken during meals with a little liquid.

Contraindication

- Known hypersensitivity to baclofen or to any of the excipients.
- Peptic ulceration.

Warnings and precautions

Psychiatric and nervous system disorders

Patients suffering from psychortic 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 or hepatic impairment.

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 only be administered to end-stage renal failure patients only if the expected benefit outweighs the potential risk (see section Dosage regimen and administration).

Lioresal should be used with extreme care in patients already receiving antihypertensive therapy. Lioresal has not significantly benefited patients with stroke. These patients has also shown poor tolerability to the drug. Safe use of Lioresal in children under age 12 has not been established, and it is, therefore, not recommended for use in children.

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 5 mg 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 haemodialysis 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 is such cases.

Laboratory test

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 diseases or diabetes mellitus, in order to ensure that no drug-induced changes in these underlying diseases have occurred.

Abrupt discontinuation

Anxiety and confusional states, delirium, hallucination, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and – as a rebound phenomenon – temporary aggravation of spasticity 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. As a precautionary measure, Lioresal administration to neonates with gradual tapering can help in controlling and preventing the withdrawal reactions (see section Pregnancy, lactation, females and males of reproductive potential).

Except in overdose-related emergencies or where serious adverse effects have occurred, the treatment should therefore 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 upright posture and balance in locomotion (see section Dosage regimen and administration).

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, or if the patient is an elderly person. 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 attacks of convulsions may occur, particularly in epileptic patients.

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

Should nausea persist following a reduction in dosage, it is recommended that Lioresal® be ingested with food or a milk beverage.

An undesirable degree of muscular hypotonia – making it more difficult for patients to walk or fend for themselves – may occur and can usually be relieved by readjusting the dosage (i.e. by reducing the doses given during the day and possibly increasing the evening dose).

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

Adverse reactions (Table 1) are listed according to system organ class in MedDRA. Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: 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 ranked in order of decreasing seriousness.

Table 1 Tabulated summary of adverse drug reactions

Nervous system disorders	
Very common:	Sedation, somnolence.
Common:	Dizziness, ataxia, tremor, headache, nystagmus.
Rare:	Paraesthesia, dysarthia, dysgeusia.
Eye disorders	
Common:	Visual impairment, accommodation disorders.
Cardiac disorders	
Common:	Diminished cardiovascular functions, dyspnea, palpitation, chest pain, syncope.Bradycardia.
Not known	
Vascular disorders	
Common:	Hypotension.
Gastrointestinal disorders	
Very common:	Nausea.
Common:	Gastrointestinal disorder, constipation, diarrhoea, retching, vomiting, anorexia, taste disorders, positive test for occult blood in stool, dry mouth.
Rare:	Abdominal pain.
Hepatobiliary disorders	
Rare:	Hepatic function abnormal.
Skin and subcutaneous tissue disorders	
Common:	Rash, hyperhidrosis.
Not known:	Urticaria.
Renal and urinary disorders	
Common:	Pollakiuria, enuresis, dysuria.
Rare:	Urinary retention, frequency of micturition, nocturia, hematuria.
Reproductive system and breast disorders	
Rare:	Erectile dysfunction, impotence, inability to ejaculate.
Respiratory, thoracic and mediastinal disorders	
Common:	Respiratory depression.
Psychiatric disorders	
Common:	Confusional state, hallucination, depression, insomnia, euphoric mood, nightmare.
Musculoskeletal and connective tissue disorders	
Common:	Muscular weakness, myalgia.

General disorders and administration site conditions	
Common:	Fatigue.
Very rare:	Hypothermia.
Not known:	Drug withdrawal syndrome* (see section Warnings and precautions)
Investigations	
Common:	Cardiac output decreased.
Not known:	Blood glucose increased.

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

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

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 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 any 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 substances passes into the breast milk, but in quantities so small that no adverse effects are to 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.

Overdosage

Signs and symptoms

Patients with renal impairment can develop signs of overdose even on low doses of oral Lioresal. 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 disorders, impaired pupillary reflex, generalized muscular hypotonia, myoclonus, hyporeflexia or areflexia, peripheral vasodilatation, hypotension or hypertension, bardycardia, 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 be given for complications such as hypotension, hypertension, convulsions, gastrointestinal disturbances and respiratory or cardiovascular depression.

Since the drug is excreted chiefly via 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). In the event of convulsions, diazepam should be administered cautiously i.v.

Clinical pharmacology

Pharmacotherapeutic group, ATC code

Antispastic with spinal site of action, ATC Code: M03BX01.

Mechanism of action (MOA)

Lioresal is a highly effective antispastic with a spinal site of action.

Baclofen depresses monosynaptic and polysynaptic reflex transmission in 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 exerts an antinociceptive effect. 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 improves the patient's mobility, makes it easier for him to manage without aid and facilitates passive and active physiotherapy.

Baclofen stimulates gastric acid secretion.

Pharmacokinetics

Absorption

Baclofen is rapidly and completely absorbed from the gastrointestinal tract.

Following oral administration of single doses of 10, 20 and 30 mg baclofen, peak plasma concentrations averaging about 180, 340 and 650 nanogram/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, amounted to about 1.140; 2.250 and 3.350 nanogram x h/ml, respectively.

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. Its serum protein-binding rate is approximately 30%.
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 faeces.

Special populations

Elderly patients (aged 65 years 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. The peak plasma concentrations of baclofen in elderly patients are slightly lower and occur later than in healthy young subjects but the AUCs are similar in the two groups.

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 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-clinical 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 doses used (50 to 100 mg/kg) were observed in female rats treated with baclofen for two years.

Pharmaceutical information

Incompatibilities

None known.

Special precautions for storage

Do not store above 30°C
Protect from heat and moisture.

Shelf-life: The expiry date is indicated on the packaging.

Package

Pack of 5 blisters of 10 tablets.

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

HARUS DENGAN RESEP DOKTER
To be dispensed only on the prescription of a physician.

Reg. No. DKL9930409110A1

Manufactured by PT Novartis Indonesia, Jakarta, Indonesia.

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