NOVARTIS

LIORESAL

(Baclofen)

10 mg and 25 mg, tablets

Professional Information

Document status: Final

Approval date: 12 May 2022

Scheduling Status: S4

1. NAME OF MEDICINAL PRODUCT

LIORESAL 10® Tablets

LIORESAL 25® Tablets

2. Qualitative and quantitative composition

LIORESAL 10®: Tablets containing 10 mg baclofen.

LIORESAL 25®: Tablets containing 25 mg baclofen

For a full list of excipients see section 6.1 – List of excipients

3. PHARMACEUTICAL FORM

LIORESAL 10®:

White to faintly yellowish, round, flat tablets with a slightly bevelled edge. One side carries the debossment “CG”, the other the debossment “K”, score, “J”. Diameter approximately 7 mm. Thickness approximately 3 mm.

LIORESAL 25®:

White to faintly yellowish, round, flat tablets with a slightly bevelled edge with the CG inscription on one side and the UR inscription with brake scored on the other side. Diameter approximately 8 mm. Thickness approximately 3.2 mm.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATION

Spasticity of the skeletal muscle due to multiple sclerosis; spastic conditions occurring in spinal-cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown aetiology – e.g. spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord.

Spasticity of cerebral origin, e.g. following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease.

4.2 POSOLOGY AND METHOD OF ADMINISTATION

Treatment should always be initiated with small, gradually increasing doses of LIORESAL. The optimum daily dosage should be individually adapted to the patient's requirements in such a way that clonus, flexor and extensor spasms, and spasticity are reduced, but that a sufficient degree of muscle tone is maintained to permit active movements and adverse effects are avoided 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.

LIORESAL should be taken during meals with a little liquid.

The daily dosage should be given in at least 3 divided doses in adults, and 3 to 4 in children.

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

Abrupt discontinuation of the treatment should be avoided (see Section 4.4.)

Adults

Treatment should, as a rule, be started with a dosage of 5 mg three times daily, which for the purpose of cautious dose titration, should subsequently be increased at three-day intervals by 5 mg three times daily until the requisite daily dosage has been attained, i.e.:

5 mg three times daily for 3 days

10 mg three times daily for 3 days

15 mg three times daily for 3 days

20 mg three times daily for 3 days

In certain patients reacting sensitively to medicines, it may be advisable to begin with a lower daily dosage (5 mg or 10 mg) and to raise this dosage more gradually. The optimum dosage generally ranges from 30 mg to 80 mg daily.

Doses of more than 80 mg to 100 mg daily are not generally recommended although higher doses have been given to carefully supervised patients in hospital.

Children

Treatment should usually be started with a very low dose, e.g. 0,3 mg/kg a day, in divided doses. The dosage should be raised cautiously, at about 1 to 2 week 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 mass. In children over 10 years of age, however, a maximum daily dosage of 2,5 mg/kg body mass may be given.

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). Patients undergoing chronic haemodialysis, baclofen concentrations in plasma are elevated and therefore a particularly low dosage of LIORESAL should be selected, i.e. approximately 5 mg daily.

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

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. However, LIORESAL has the potential of elevating liver enzymes. LIORESAL should be prescribed with caution in patients with hepatic impairment

4.3 CONTRAINDICATIONS

- Known hypersensitivity to baclofen or to any of the excipients.
- Porphyria.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

LIORESAL may be associated with dizziness, sedation, somnolence, visual disturbances and impaired concentration which may impair the patient's reaction and may be aggravated by the simultaneous intake of alcohol or central nervous system depressant agents.

Patients experiencing these adverse reactions should be advised to refrain from driving or using machines**.**

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 exacerbations of these conditions may occur.

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

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 over-dosage. Adequate anticonvulsive therapy should be continued and the patient carefully monitored.

LIORESAL should be used with caution in patients with, or with a history of, peptic ulcers, as well as in those suffering from cerebrovascular diseases or from respiratory, hepatic, or renal failure. Patients with stroke tolerate LIORESAL poorly.

LIORESAL should be used with caution in patients with pre-existing sphincter hypertonia as acute retention of urine may occur.

In instances, elevated aspartate aminotransferase (AST), alkaline phosphatase (ALP), and 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.

Renal Impairment

LIORESAL should be used with caution in patients with renal impairment (see section 4.2).

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 4.9).

Particular caution is required when combining LIORESAL with 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. 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, hallucinations, psychotic, manic or paranoid states, convulsions (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis 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. As a precautionary measure, LIORESAL administration to neonates with gradual tapering can help in controlling and preventing the withdrawal reactions (See section 4.6)

Except in overdose - related emergencies or where serious adverse effects have occurred, treatment should therefore always be gradually discontinued by successively reducing the dosage (over a period of approximately one to two weeks).

LIORESAL tablets contain wheat starch. Wheat starch may contain gluten, but only in trace amounts. Taking LIORESAL tablets is therefore considered safe for people with celiac disease.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Where LIORESAL is taken concomitantly with other medicines acting on the CNS, with synthetic opiates or with alcohol, increased sedation may occur. The risk of respiratory depression is also increased. Careful monitoring of respiratory and cardiovascular functions is essential especially in patients with cardiopulmonary disease and respiratory muscle weakness.

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

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

In patients with Parkinson's disease receiving treatment with LIORESAL and levodopa, (alone or in combination with dopa-decarboxylase (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.

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

Drugs or medicinal products that can significantly impact renal function may reduce baclofen excretion leading to toxic effects

4.6 FERTILITY, PREGNANCY AND LACTATION

There are no adequate and well-controlled studies in pregnant women. Baclofen crosses the placental barrier and should not be used during pregnancy.

Drug withdrawal reactions including postnatal convulsions in neonates have been reported after intra-uterine exposure to oral LIORESAL (see section 4.4)

Breast-feeding

In mothers taking LIORESAL in therapeutic doses, the active substance passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected

Fertility

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

4.7 Effects on the ability to drive and use Machines

LIORESAL may cause dizziness, sedation, somnolence and visual impairment (see section 4.8) which may impair the patient’s reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines

LIORESAL can have a major influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

Unwanted effects occur mainly at the start of treatment (e.g. sedation, somnolence, drowsiness, fatigue and nausea), if the dose is raised too rapidly, if large doses are employed, or if the patient is an elderly person. In patients with a case history of psychiatric illness or with cerebrovascular disorders (e.g. stroke), as well as in elderly patients, adverse reactions may assume a more serious form.

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

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

Many of the adverse CNS and genitourinary effects reported are known to occur in association with the underlying conditions being treated.

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

Adverse reactions (Table 1) 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), including isolated reports.

Table 1

Nervous System disorders	
Very Common:	Sedation, somnolence, drowsiness, fatigue and nausea.
Common:	Dryness of the mouth, respiratory depression, exhaustion, mental confusion, dizziness, headache, insomnia, euphoria, depressive states, myalgia, muscular weakness, ataxia, tremor, nystagmus, hallucinations, nightmares, fatigue
Rare:	Paraesthesia, dysarthria, dysgeusia.
Eye Disorders	
Common:	Accommodation disorders, visual impairment
Uncommon:	Tinnitus
Cardiac disorders	
Common:	Cardiac output decreased
Not known:	Bradycardia
Vascular disorders	
Common:	Hypotension
Gastrointestinal disorders	
Very common:	Nausea
Common:	Gastrointestinal disorders, retching, vomiting, constipation, diarrhoea.
Hepatobiliary disorders	
Rare:	Hepatic function abnormal

Skin and subcutaneous tissue disorders	
Common:	Hyperhydrosis, rash
Not known:	Urticaria
Renal and urinary disorders	
Common:	Pollakiuria, enuresis, dysuria.
Rare:	Urinary retention
Reproductive system and breast disorders	
Rare:	Erectile dysfunction.
General disorders and administration site conditions	
Very Rare:	Hypothermia
Not known:	Drug withdrawal syndrome
Investigations	
Not known:	Blood glucose increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions allows continued monitoring of the benefit/risk balance of LIORESAL. Healthcare professionals are asked to report any suspected adverse reactions via patientsafety.sacg@novartis.com and via the “6.04 Adverse Drug Reaction Reporting Form” found online under SAHPRA`s publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 OVERDOSAGE

Prominent features are signs of central nervous depression: drowsiness, impairment of consciousness, respiratory depression, coma. Also liable to occur are: confusion, hallucinations, agitation, accommodation disorders, absent pupillary reflex; generalised muscular hypotonia, myoclonia, hyporeflexia or areflexia; convulsions; peripheral vasodilatation, hypotension or hypertension, bradycardia or tachycardia; hypothermia; nausea, vomiting, diarrhoea, hypersalivation; elevated LDH, AST, and AP values, sleep apnea, rhabdomyolysis.

A deterioration in the condition may occur if various substances or medicines 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.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification

A 2.10 Centrally active muscle relaxants.

Pharmacodynamic properties

Baclofen displays pronounced muscle-relaxing activity. It acts on the motor system of the spinal cord in a distinctive segmental fashion. Baclofen inhibits both mono- and polysynaptic reflex transmission and reduces the activity of the gamma motor neurones. It does not, however, influence neuromuscular

impulse transmission in the motor endplates. In neurological diseases associated with skeletal muscle spasm Baclofen reduces spasticity. It also markedly relieves the associated pain, rigidity, automatism and clonus, with consequent improvement in the patient's mobility. Active and passive physiotherapy are thereby facilitated.

Baclofen stimulates gastric acid secretion.

Pharmacokinetic properties

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 h. The corresponding areas under the serum concentration curves (AUCs) are proportional to the size of the dose

The distribution volume of baclofen amounts to 0.7 L/kg. The protein-binding rate 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.

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

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 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

Pediatric patients

Following oral administration of 2.5 mg baclofen tablet in children (aged 2 to12 years), Cmax of 62.8±28.7 nanogram/mL, and Tmax in the range of 0.95-2 h 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 (T1⁄2) of 5.10 h have been reported.

Hepatic impairment

No pharmacokinetic data is available in patients with hepatic impairment after administration of baclofen. However, as 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 baclofen. Baclofen is predominantly eliminated unchanged in urine. Sparse plasma concentration data collected only in female patients under chronic haemodialysis 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 renal impairment patients, and prompt haemodialysis is an effective means of reversing excess baclofen in systemic circulation.

6. PHARMACEUTICAL PARTICULARS

6.1 EXCIPIENTS

silica aerogel; cellulose microcrystalline; magnesium stearate; polyvidone; wheat starch.

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF-LIFE

Lioresal 10 mg: 36 months

Lioresal 25 mg: 48 Months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at or below 30 °C and protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

LIORESAL is supplied as uncoated tablets of 10 mg and 25 mg in packs of 30.

6.6 Special precautions for disposal and other handling

No special requirements

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATES OF REGISTRATION

NOVARTIS SOUTH AFRICA (PTY) LTD

Magwa Crescent West,

Waterfall City,

Jukskei View,

Johannesburg

2090

8. REGISTRATION NUMBERS

LIORESAL 10 mg® Tablets: E/2.10/227

LIORESAL 25 mg® Tablets: E/2.10/228

DATE OF FIRST AUTHORISATION

Lioresal 10 mg: 16 April 1973

Lioresal 25 mg: 16 April 1973

DATE OF REVISION OF THE TEXT

12 May 2022