NOVARTIS

Drug Regulatory Affairs

LIORESAL® (baclofen)

5 mg, 10 mg and 25 mg Tablets

1 mg/mL Syrup

Basic Prescribing Information

NOTICE

The Basic Prescribing Information (BPI) is the Novartis Core Data Sheet. It displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

National Prescribing Information is based on the BPI. However, because regulatory requirements and medical practices vary between countries, National Prescribing Information (incl. US Package Insert or European SPCs) may differ in several respects, including but not limited to the characterisation of risks and benefits.

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1 Name of the medicinal product

LIORESAL® 5 mg, 10 mg and 25 mg scored tablets, 1 mg/mL syrup.

2 Qualitative and quantitative composition

Active substance: beta-(Aminomethyl)-p-chlorohydrocinnamic acid (= baclofen), a racemic mixture of the R,(-) and S, (+) isomers.

Lioresal® scored tablets: 5 mg, 10 mg or 25 mg of baclofen.

Lioresal syrup: 1 mg/mL of baclofen.

For a full list of excipients, see section 6.1 List of excipients.

3 Pharmaceutical form

Tablet, scored

Syrup

Information might differ in some countries.

4 Clinical particulars

4.1 Therapeutic indications

Spasticity of the skeletal muscles in multiple sclerosis. Spastic conditions occurring in spinal-cord diseases of infectious, degenerative, traumatic, neoplastic, or unknown origin: e.g. spastic spinal paralysis, amyotrophic lateral sclerosis, syringomyelia, transverse myelitis, traumatic paraplegia or paraparesis, and compression of the spinal cord; muscle spasm of cerebral origin, as well as following cerebrovascular accidents or in the presence of neoplastic or degenerative brain disease [3,13,14,22,30-32,48-50].

Paediatric population (0-<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 [102].

4.2 Posology and method of administration

Treatment should always be initiated with small, gradually increasing doses of Lioresal [14,22,23,30]. The lowest dose compatible with an optimal response is recommended [101]. The optimum daily dosage should be individually adapted to the patient's requirements [66] in such a way that clonus, flexor and extensor spasms and spasticity are reduced, but adverse effects are as far as possible avoided [3,13,20,22,23,31,63].

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 [26,60]. It may be important to maintain some degree of muscle tone and allow occasional spasms to help support circulatory function [64].

Lioresal should be taken during meals with a little liquid [22,23].

If no benefit is apparent within 6 to 8 weeks of achieving the maximum dosage, a decision whether to continue with Lioresal should be taken [63].

Adults

Treatment should be started with a dosage of 15 mg daily, preferably in 2 to 4 divided doses [3,13,14,101],which - for the purpose of cautious dose titration - should subsequently be increased by 15 mg/day increments at 3-day intervals until the requisite daily dosage has been attained [3,13,14,22,23,101]. 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. The optimum dosage generally ranges from 30 to 80 mg daily. Daily doses of 100 to 120 mg may be given to carefully supervised patients in hospital [23,60,63,65,66].

Paediatric population (0-<18 years)

Treatment should usually be started with a very low dose (corresponding to approximately 0.3 mg/kg a day), preferably in 2 to 4 divided doses [3,13,14,101]. Therefore, Lioresal tablets are not suitable for use in children below 33 kg body weight [101].

The dosage should be raised cautiously, at about 1 week intervals, until it becomes sufficient for the child's individual requirements [102].

The usual daily dosage for maintenance therapy ranges between 0.75 and 2 mg/kg body weight [46,47]. 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 [50,101].

Renal impairment

In patients with **impaired renal function** Lioresal should be given with caution and in lower doses [2,19,26,29]. In patients undergoing chronic haemodialysis, baclofen concentrations in plasma are elevated and therefore a particularly low dosage of Lioresal should be selected, i.e. approx. 5 mg daily [45].

Lioresal should only be administered to end stage renal failure patients when benefit outweighs risk. These patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy) (see section 4.4 Special warnings and precautions for use and section 4.9 Overdose) [100].

Elderly and patients with spastic states of cerebral origin

Since unwanted effects are more likely to occur in **elderly patients** or in patients with **spastic states of cerebral origin** [13,19], it is recommended that a very cautious dosage schedule be adopted in such cases and that the patient be kept under appropriate surveillance.

4.3 Contraindications

Known hypersensitivity to baclofen or to any of the excipients.

4.4 Special warnings and precautions for use

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 exacerbations of these conditions may occur [19,20,21,51,67-69].

Epilepsy

Special attention should be given to patients known to suffer from epilepsy since lowering of the convulsion threshold may occur [26] and seizures have occasionally been reported in connection with the discontinuation of Lioresal [27,70] or with overdosage [71]. Adequate anticonvulsive therapy should be continued and the patient carefully monitored [3,37,72,73].

Others

Lioresal should be used with caution in patients with, or with a history of, peptic ulcers [20,58], as well as in those suffering from cerebrovascular diseases [20,23] or from respiratory [19,20,23] or hepatic [23] insufficiency.

Paediatric population

There is very limited clinical data on the use of Lioresal in children under the age of one year. [102].

Renal impairment

Lioresal should be used with caution in patients with renal insufficiency [19,20,23] and should only be administered to end stage renal failure patients when benefit outweighs risk (See section 4.2 Posology and method of administration) [100].

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 [100].

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 [100].

Urinary disorders

Under treatment with Lioresal neurogenic disturbances affecting emptying of the bladder may show an improvement [55,59,62]. In patients with pre-existing sphincter hypertonia acute retention of urine may occur; the drug should be used with caution in such cases [63].

Laboratory tests

In rare instances, elevated SGOT, alkaline phosphatase and glucose levels in the serum have been recorded [21,26,32]. 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 [26].

Excipients

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.

Lioresal syrup contains methylparaben and propylparaben, which may cause allergic reactions (possibly delayed), and exceptionally difficulties in breathing with wheezing or coughing. Lioresal syrup contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine. Lioresal syrup also contains 1.6 mg of sodium per 1 mL of syrup.

Abrupt discontinuation

Anxiety [24] and confusional states [27,67], hallucinations [13,19-21,25-27,74], psychotic [28], manic [19,61] or paranoid [26,67] states, convulsions (status epilepticus) [21,22,26,27,33], dyskinesia [25,28], tachycardia [24,39,74], hyperthermia [75] and - as a rebound phenomenon - temporary aggravation of spasticity [13,25] have been reported following the abrupt withdrawal of Lioresal, especially after long-term medication.

Postnatal convulsions have been reported after intrauterine exposure to oral Lioresal [103] (See section 4.6 Pregnancy and lactation).

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 [97].

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) [19,20,26,66].

4.5 Interaction with other medicinal products and other forms of interaction

Where Lioresal is taken concomitantly with other drugs acting on the CNS, with synthetic opiates [57] or with alcohol, increased sedation may occur [13,26] (see section 4.7 Effects on ability to drive or use machines). The risk of respiratory depression is also increased [76]. 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 [21,34].

Since concomitant treatment with antihypertensives is likely to enhance the fall in blood pressure, the dosage of antihypertensive medication should be adjusted accordingly [20,23]. Hypotension has been reported in one patient receiving morphine and intrathecal baclofen.

In patients with Parkinson's disease receiving treatment with Lioresal and levodopa, there have been reports of mental confusion, hallucinations, headaches, nausea and agitation [43,51].

Drugs or medicinal products that can significantly impact renal function may reduce baclofen excretion leading to toxic effects (see section 4.4 Special warnings and precautions for use) [100].

4.6 Pregnancy and lactation

Pregnancy

Lioresal given orally has been shown to increase the incidence of omphaloceles (ventral hernias) in foetuses of rats given approximately 13 times the maximum oral dose (on a mg/kg basis) recommended for human use [77,78]. This abnormality was not seen in mice or rabbits [78-80].

There are no adequate and well-controlled studies in pregnant women. Baclofen crosses the placental barrier [41] and should not be used during pregnancy unless the potential benefit outweighs the potential risk to the foetus.

One case of suspected withdrawal reaction (generalised convulsions) has been reported in a week-old infant whose mother had taken baclofen during pregnancy. The convulsions, which were refractory to standard anticonvulsant treatment, ceased within 30 minutes of giving baclofen to the infant [103].

Lactation

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 [36,40].

4.7 Effects on ability to drive and use machines

Lioresal may be associated with dizziness, sedation, somnolence and visual disturbance (see section 4.8 Undesirable effects) which may impair the patient's reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines [13,20,23].

4.8 Undesirable effects

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 [98].

Unwanted effects occur mainly at the start of treatment (e.g. sedation, somnolence) [23,50], if the dose is increased too rapidly [23,26,32], or if large doses are employed [30]. They are often transitory [26,32] and can be attenuated or eliminated by reducing the dosage [13,23]; they are seldom severe enough to necessitate withdrawal of the medication [13,14]. In patients with a 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 [19,21,23].

Lowering of the convulsion threshold and convulsions may occur, particularly in epileptic patients [2,13,26,32,38].

Certain patients have shown increased muscle spasticity as a paradoxical reaction to the medication [22].

Many of the side effects reported are known to occur in association with the underlying conditions being treated [3,26].

Table 1

Nervous system disorders	
Very common:	Sedation [3,22,23,50], somnolence [13,14,20,26,29,30,60].
Common:	Respiratory depression [13], light-headedness [14], lassitude [26], exhaustion [3], confusional state [3,19,23,26,29,30,43], dizziness [3,23,26,29], headache [20,23,26,60], insomnia [20,26,29], euphoric mood [3,19,20,23,23,60], depression [3,19,20,23,26,60,81], muscular weakness [3,26,29], ataxia [13,26], tremor [20,26], hallucinations [13,23,24,26,30,43,60], nightmares [60], myalgia, nystagmus [26], dry mouth [14].
Rare:	Paraesthesia [26,63], dysarthria [82,87], dysgeusia [23].
Very rare:	Hypothermia [99].
Eye disorders	
Common:	Accommodation disorders [26], visual disturbances [20,23,60].
Cardiac disorders	
Common:	Cardiac output decreased [13].
Vascular disorders	
Common:	Hypotension [20,21,26,29].
Gastrointestinal disorders	
Very common:	Nausea [3,14,20,22,23,26,30,50,60].
Common:	Gastrointestinal disturbance [26], retching, vomiting [3,20,30,50], constipation [20,26], diarrhoea [20,23,26,50].
Rare:	Abdominal pain [85,87].
Hepatobiliary disorders	
Rare:	Hepatic function abnormal [20].
Skin and subcutaneous tissue disorders	
Common:	Hyperhidrosis [23], rash [20,23,26,29].
Unknown:	Urticaria [104].
Renal and urinary disorders	
Common:	Pollakiuria [26], enuresis [26], dysuria [26].
Rare:	Urinary retention [83,86,87].
Reproductive system and breast disorders	
Rare:	Erectile dysfunction [84,87].

4.9 Overdose

Signs and symptoms

Prominent features are signs of central nervous depression [26,35,52]: drowsiness [13,54] impairment of consciousness [35,52-54,88], coma [2,24,35,53,54,56], respiratory depression [2,13,24,52-54,56,88].

Also liable to occur are: confusion [35,54] hallucinations [35,54], agitation [54], convulsions [2,52,54], EEG changes (burst suppression pattern and triphasic waves) [100], accommodation disorders [54], absent pupillary reflex [53,54], generalised muscular hypotonia [13,35,52-54,88], myoclonia [24], hyporeflexia [56,88] or areflexia [52-54], peripheral vasodilation [54], hypotension [53,54] or hypertension [98], bradycardia [52-54,56], tachycardia [98] or cardiac arrhythmias [100], hypothermia [53,54], nausea [42,54], vomiting [54], diarrhoea [54], hypersalivation [42,53,54], elevated liver enzymes [42,54].

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 [54].

Treatment

No specific antidote is known [26,35].

Supportive measures and symptomatic treatment should be given for complications such as hypotension, hypertension, convulsions, gastrointestinal disturbances, and respiratory [13,26,35,52] or cardiovascular depression [26].

After ingestion of a potentially toxic amount, activated charcoal should be considered, especially during the early period after ingestion. Gastric decontamination (e.g. gastric lavage [52,53]) should be considered in individual cases, especially in the early period (60 minutes) after ingestion of a potentially life-threatening overdose. Comatose or convulsing patients should be intubated prior to the initiation of gastric decontamination [98].

Since the drug is excreted chiefly via the kidneys, generous quantities of fluid should be given, possibly together with a diuretic [35]. Haemodialysis (some times unscheduled) may be useful in severe poisoning associated with renal failure (see section 4.4 Special warnings and precautions for use) [100]. In the event of convulsions, diazepam should be administered cautiously i.v. [25,52,54].

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antispastic with spinal site of attack, ATC Code: M03B X01.

Lioresal is a highly effective antispastic with a spinal site of attack [1-3,5,13,26]. 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 [2-7,64].

Neuromuscular transmission is not affected by baclofen [8,26]. Baclofen exerts an antinociceptive effect [3,5,9-13,26]. 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 marked relief from painful spasm, automatism, and clonus. Lioresal improves the patient's mobility, facilitating management of daily activities (including catheterisation) and physiotherapy [3,13,14,64]. Prevention and healing of decubitus ulcers, and improvement in sleep patterns (due to elimination of painful muscle spasms) and in bladder and sphincter function have also been observed as indirect effects of treatment with Lioresal, leading to a better quality of life for the patient [3,13,14].

Baclofen stimulates gastric acid secretion [44,58].

5.2 Pharmacokinetic properties

Absorption

Baclofen is rapidly and completely absorbed from the gastrointestinal tract [15,17,18,89].

No significant difference between syrup and tablet formulation is observed in respect of t_{max}, C_{max}, and bioavailability [89].

Following oral administration of single doses of 10, 20, and 30 mg baclofen, peak plasma concentrations averaging about 180, 340, and 650 ng/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 [15,17,18,89].

Distribution

The distribution volume of baclofen amounts to 0.7 L/kg and the protein-binding rate is approx. 30% [15]. In the cerebrospinal fluid the active substance attains concentrations approx. 8.5 times lower than in the plasma [16].

Biotransformation

Baclofen is metabolised to only a minor extent. Deamination yields the main metabolite, beta-(p-chlorophenyl)-4-hydroxybutyric acid, which is pharmacologically inactive [15,17].

Elimination/Excretion

The plasma elimination half-life of baclofen averages 3 to 4 hours [15]. Baclofen is excreted largely in unchanged form. Within 72 hours approx. 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 [15,17].

Characteristics in patients

The pharmacokinetics of baclofen in elderly patients are virtually the same as in young subjects [90].

5.3 Preclinical safety data

Experimental evidence to date suggests that baclofen does not possess either carcinogenic or mutagenic potential [91-95].

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 [91].

6 Pharmaceutical particulars

6.1 List of excipients

Tablets: silica aerogel; cellulose microcryst.; magnesium stearate; polyvidone; wheat starch.

In addition, for 5 mg tablets only: yellow iron oxide (E 172).

Syrup: methylparahydroxybenzoate; propylparahydroxybenzoate; raspberry flavour; sodium carboxymethyl cellulose; sorbitol; purified water.

Information might differ in some countries.

6.2 Incompatibilities

None known.

6.3 Shelf life

Tablets 5 mg: 3 years.

Tablets 10 and 25 mg: 4 years.

Syrup: 3 years.

Information might differ in some countries.

6.4 Special precautions for storage

Tablets: Protect from heat and moisture (store below 25°C).

Syrup: Protect from heat and light (store below 30°C).

Information might differ in some countries.

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

6.5 Nature and contents of container

Country specific.

6.6 Instructions for use/handling

There are no specific instructions for use/handling.

This is a non-referenced document.