NOVARTIS

1. NAME OF THE MEDICINAL PRODUCT

Lioresal® Tablets 10mg
Lioresal® Tablets 25mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is: Baclofen = (β-(Aminomethyl)-p-chlorohydrocinnamic acid a racemic mixture of the R,(-) and S, (+) isomers).
One tablet contains 10mg baclofen
One tablet contains 25mg baclofen

Excipient(s) with known effect:
Wheat starch (containing gluten)

For excipients see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lioresal is indicated for muscle spasticity of various origins.

4.2 Posology and method of administration

Dosage

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 individualized in such a way that clonus, flexor and extensor spasms and spasticity are reduced, but 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.

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 (see Section 4.4).

Adults:

Treatment should be started with a dosage of 15 mg daily, preferably in 2 to 4 divided doses. 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 4.4 Warnings and Precautions). 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.

Special populations

Elderly patients (aged 65 years or above):

Since unwanted 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.

Paediatric population (0 to < 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. Therefore, Lioresal tablets are not suitable for use in children below 33 kg body weight.

The dosage should be raised cautiously, at about 1 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 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.

Patients with impaired renal function:

In patients with impaired renal function Lioresal should be given with caution and in lower doses. 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.
Lioresal should be administered to end stage renal failure patients only if the expected benefit outweighs the potential 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 and section 4.9).

Patients with hepatic impairment:

No studies have been performed in patients with hepatic impairment receiving Lioresal therapy. The liver does not play a significant role in the metabolism of baclofen after oral administration of Lioresal (see section 5.2). However, Lioresal has the potential of elevating liver enzymes. Lioresal should be prescribed with caution in patients with hepatic impairment.

Patients with spastic states of cerebral origin:

Since unwanted 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.

<u>Method of administration</u>
Lioresal should be taken during meals with a little liquid.

4.3 Contraindications

- Hypersensitivity to baclofen or to any of the excipients listed in section 6.1
- Peptic ulceration.

4.4 Special warnings and precautions for use

Psychiatric and nervous system disorders
Psychotic disorders, schizophrenia, depressive or manic disorders, confusional states or Parkinson's disease may be exacerbated by treatment with Lioresal. Patients suffering from these conditions should therefore be treated cautiously and kept under close surveillance.

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 drug therapy. 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.

Cases of misuse, abuse and dependence have been reported with baclofen. Caution should be exercised in patients with a history of substance abuse and the patient should be monitored for symptoms of baclofen misuse, abuse or dependence e.g. dose escalation, drug-seeking behaviour, development of tolerance.

Epilepsy
Lioresal may also exacerbate epileptic manifestations but can be employed provided appropriate supervision and adequate anticonvulsive therapy are maintained.

Others
Lioresal should be used with extreme care in patients already receiving antihypertensive therapy, (see section 4.5).

Lioresal should be used with caution in patients suffering from cerebrovascular accidents or from respiratory or hepatic impairment.

Since unwanted effects are more likely to occur, a cautious dosage schedule should be adopted in elderly and patients with spasticity of cerebral origin (see section 4.2).

Renal impairment
Baclofen should be used with caution in patients with renal impairement and should be administered to end stage renal failure patients only if the expected benefit outweighs the potential risk (See section 4.2 Posology and method of administration). Neurological signs and symptoms of overdose including clinical manifestations of toxic encephalopathy (e.g. confusion, disorientation, somnolence and depressed level of consciousness) have been observed in patients with renal impairment taking oral baclofen at doses of more than 5mg per day and at doses of 5mg per day in patients with end stage renal failure being treated with chronic hemodialysis. Patients with impaired renal function should be closely monitored for prompt diagnosis of early symptoms of toxicity.

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

Cases of baclofen toxicity have been reported in patients with acute renal failure (see section 4.9).

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.

Urinary disorders
Under treatment with Lioresal neurogenic disturbances affecting 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 serum have been recorded. Appropriate laboratory tests should be performed in patients with liver diseases or diabetes mellitus in order to ensure that no drug induced changes in these underlying diseases have occurred.

Excipients
Lioresal tablets contain wheat starch (containing gluten). The very low levels of gluten are very unlikely to cause problems in patients with coeliac disease. Patients with a wheat allergy (different from coeliac disease) should not take this medicine.

Each 10 mg tablet contains 61.0 mg wheat starch.
Each 25 mg tablet contains 83.0 mg wheat starch.

Abrupt withdrawal:
Treatment should always, (unless serious adverse effects occur), be gradually discontinued by successively reducing the dosage over a period of about 1-2 weeks. Anxiety and confusional state, delirium, hallucination, psychotic disorder, mania or paranoia, convulsion (status epilepticus), dyskinesia, tachycardia, hyperthermia, rhabdomyolysis and temporary aggravation of spasticity and hypertonia have been reported with 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 4.6).

Treatment should always, (unless serious adverse effects occur), therefore be gradually discontinued by successively reducing the dosage over a period of about 1-2 weeks.

Paediatric patients
There is very limited clinical data on the use of Lioresal in children under the age of one year. Use in this patient population should be based on the physician's consideration of individual benefit and risk of therapy.

Posture and balance
Lioresal should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interaction

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, nausea and agitation. Worsening of the symptoms of

Parkinsonism has also been reported. Hence, caution should be exercised during concommitant 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 section 4.7).

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 Lioresal and 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 affect renal function may reduce baclofen excretion leading to toxic effects (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
During pregnancy, especially in the first 3 months, Lioresal should only be employed if its use is of vital necessity. The benefits of the treatment for the mother must be carefully weighed against the possible risks for the child. Baclofen crosses the placental barrier.

Foetal/neonatal adverse reactions
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 at therapeutic doses, the active substance passes into the breast milk, but in quantities so small that no undesirable effects in the infant are to be expected.

4.7 Effects on ability to drive and use machines

Lioresal may be associated with adverse effects such as 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.

4.8 Undesirable effects

Adverse effects occur mainly at the start of treatment (e.g. sedation, somnolence and nausea), if the dosage is raised too rapidly, if large doses are employed, or in elderly patients. They are often transitory and can be attenuated or eliminated by reducing the dosage; they are seldom severe enough to necessitate withdrawal of the medication.

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

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.

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

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

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 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) and Not known (cannot be estimated from the available data).

Table 1 Tabulated summary of adverse drug reactions

Immune system disorders	
Not known:	Hypersensitivity
Nervous system disorders	
Very common:	Sedation, somnolence
Common:	Respiratory depression, confusional state, dizziness, hallucination, depression, fatigue, insomnia, euphoric mood, muscular weakness, ataxia, tremor, nightmare, myalgia, headache, nystagmus, dry mouth
Rare:	Paraesthesia, dysarthria, dysgeusia
Unknown:	Sleep Apnoea syndrome*
Eye disorders	
Common:	Visual impairment, accommodation disorder
Cardiac disorders	
Common:	Cardiac output decreased
Not known:	Bradycardia
Vascular disorders	
Common:	Hypotension
Gastrointestinal disorders	
Very common:	Nausea
Common:	Gastrointestinal disorder, constipation, diarrhoea, retching, vomiting
Rare:	Abdominal pain
Hepatobiliary disorders	
Rare:	Hepatic function abnormal

Skin and subcutaneous tissue disorders	
Common:	Rash, hyperhidrosis
Not known	Urticaria, alopecia
Renal and urinary disorders	
Common:	Pollakiuria, enuresis, dysuria
Rare:	Urinary retention
Reproductive system and breast disorders	
Rare:	Erectile dysfunction
Not known:	Sexual dysfunction
General disorders and administration site conditions	
Very rare	Hypothermia
Not known	Drug withdrawal syndrome* (see section 4.4) , swelling face and peripheral oedema
Investigations	
Not known:	Blood glucose increased

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

* Cases of central sleep apnoea syndrome have been observed with baclofen at high doses (≥ 100 mg) in patients who are alcohol dependent.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Symptoms: Prominent features are signs of central nervous depression: somnolence, depressed level of consciousness, coma, respiratory depression and tinnitus. Also liable to occur are: confusion, hallucination, agitation, convulsion, abnormal electroencephalogram (burst suppression pattern and triphasic waves), accommodation disorder, impaired pupillary reflex, generalised muscular hypotonia, myoclonus, hyporeflexia or areflexia, peripheral vasodilatation, hypotension or hypertension, bradycardia, tachycardia or cardiac arrhythmia, hypothermia, nausea, vomiting, diarrhoea, salivary hypersecretion, increased hepatic enzymes and rhabdomyolysis. Patients with renal impairment can develop signs of overdose even on low doses of oral Lioresal (see section 4.2 and section 4.4).

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.

Treatment: No specific antidote is known.

Supportive measures and symptomatic treatment should be given for complications such as hypotension, hypertension, convulsions, gastrointestinal disorders 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. Haemodialysis (sometimes unscheduled) may be useful in severe poisoning associated with renal failure (see section 4.4).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antispastic with spinal site attack, ATC code: M03B X01

Lioresal is an antispastic agent acting at the spinal level. A gamma-aminobutyric acid (GABA) derivative, Lioresal is chemically unrelated to other antispastic agents.

Lioresal depresses monosynaptic and polysynaptic reflex transmission, probably by stimulating the $GABA_B$-receptors, this stimulation in turn inhibiting the release of the excitatory amino acids glutamate and aspartate. Neuromuscular transmission is unaffected by Lioresal.

The major benefits of Lioresal stem from its ability to reduce painful flexor spasms and spontaneous clonus thereby facilitating the mobility of the patient, increasing his independence and helping rehabilitation.

Lioresal also exerts an antinociceptive effect. General well being is often improved and sedation is less often a problem than with centrally acting drugs.
Baclofen stimulates gastric acid secretion.

5.2 Pharmacokinetic properties

Absorption: Lioresal (baclofen) is rapidly and completely absorbed from the gastro-intestinal tract. No significant difference between the liquid and tablet formulations is observed in respect of T_{max}, C_{max} and bioavailability. Following oral administration of single doses (10-30mg) peak plasma concentrations are recorded after 0.5 to 1.5 hours and areas under the serum concentration curves are proportional to the dose.

Distribution: The volume of distribution of baclofen is 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 cerebrospinal fluid active substance concentrations are approximately 8.5 times lower than in the plasma.

Biotransformation: Baclofen is metabolised to only a minor extent. Deamination yields the main metabolite, β-(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 eliminated largely in unchanged form. Within 72 hours, approximately 75% of the dose is excreted via the kidneys with about 5% of this amount as metabolites.

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.

Paediatric patients

Following oral administration of 2.5 mg Lioresal 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 ($T_{½}$) of 5.10 h have been reported.

Hepatic impairment
No pharmacokinetic data are 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 renal impairment patients, and prompt hemodialysis is an effective means of reversing excess baclofen in systemic circulation.

5.3 Preclinical safety data

Baclofen increases the incidence of omphaloceles (ventral hernias) in the foetuses of rats given approximately 13 times the maximum oral dose (on a mg/kg basis) recommended for human use. This was not seen in mice or rabbits.

An apparently dose related increase in the incidence of ovarian cysts, and a less marked increase in enlarged and/or haemorrhagic adrenals have been observed in female rats treated for 2 years. The clinical relevance of these findings is not known.

Experimental evidence to date suggests that baclofen does not possess either carcinogenic or mutagenic properties.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets: wheat starch; cellulose microcrystaline; povidone; silica colloidal anhydrous; magnesium stearate.
Lioresal tablets contain wheat starch. Each 10 mg tablet contains 61.0 mg wheat starch. Each 25 mg tablet contains 83.0 mg wheat starch.

6.2 Incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging matierials.

6.4 Special precautions for storage

Lioresal 10mg-Store below 30°C
Lioresal 25mg-Store below 25°C

Lioresal tablets should be protected from moisture. Store in the original package.
Lioresal must be kept out of reach and sight of children.

6.5 Nature and contents of container

Tablets 10mg: circular, flat, white to faint yellowish tablets, uncoated, with bevelled edges, having the monogram “CG” on one side and the letters “KJ” and a break line on the other.
Tablets 25mg: white to slightly yellowish, flat, round and bevelled edge tablets, with “CG” inscription on one side and “UR” inscription with break-scored on the other side. The break-line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

In PVC/PE/PVDC blister, packs of 50 tablets.

6.6 Instructions for use/handling

There is no specific instruction for use/handling.

7. Registration Holder and Importer and its address:

Novartis Israel Ltd.,
P.O.B. 7126, Tel Aviv

8. Registration Number:

Lioresal 10mg: 120-93-23361
Lioresal 25mg: 124-09-23362

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