PRODUCT MONOGRAPH

Pr LIORESAL®
(baclofen)
10 mg and 20 mg Tablets

Antispastic Agent

Novartis Pharmaceuticals Canada Inc.
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DATE OF REVISION
May 7, 2020

Control # 235825

NAME OF DRUG

PrLIORESAL®

(baclofen)

10 mg and 20 mg Tablets

THERAPEUTIC CLASSIFICATION

Antispastic Agent

CLINICAL PHARMACOLOGY

Mechanism of action (MOA)

The precise mechanisms of action of LIORESAL (baclofen) are not fully known. It inhibits both monosynaptic and polysynaptic reflexes at the spinal level, probably by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although LIORESAL is an analog of the putative inhibitory neurotransmitter gamma-aminobutyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects.

Peak plasma concentrations of LIORESAL are achieved within 2 hours and the plasma half-life is 2-4 hours.

Special populations

Geriatrics (aged 65 years or above)

Following a single oral dose, elderly patients have a slower rate of absorption and elimination, a slightly prolonged elimination half-life, but a similar systemic exposure of baclofen compared to young adults.

Hepatic impairment

No pharmacokinetic data is available in patients with hepatic impairment after administration of LIORESAL. 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 LIORESAL. Baclofen is predominantly eliminated unchanged in urine. Sparse plasma concentration data collected in female patients under chronic hemodialysis or compensated renal failure indicate significantly decreased clearance and increased half-life of baclofen in these patients. Severe neurological outcomes have been reported in patients with renal impairment after oral administration, thus LIORESAL should be given with special care and caution in these patients (see WARNINGS, Renal Impairment).

INDICATIONS

LIORESAL (baclofen) is useful for the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis.

LIORESAL may also be of some value in patients with spinal cord injuries and other spinal cord diseases.

CONTRAINDICATIONS

Hypersensitivity to LIORESAL (baclofen) or to any of the excipients.

WARNINGS

SERIOUS WARNINGS AND PRECAUTIONS

Life-threatening Respiratory Depression

Concomitant use of LIORESAL with opioids may result in respiratory depression, profound sedation, syncope, and death.

- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

Abrupt Drug Withdrawal:

Following abrupt withdrawal of LIORESAL (baclofen), delirium, visual and auditory hallucinations, convulsion (status epilepticus), dyskinesia, confusional state, psychotic disorder, mania or paranoia, anxiety with tachycardia and sweating, insomnia, rhabdomyolysis and worsening of spasticity have occurred. Therefore, except for serious adverse reactions, the dose should be reduced slowly when the drug is discontinued (over a period of approximately 1-2 weeks).

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.

Neonatal Withdrawal:

Drug withdrawal reactions including, irritability, high-pitched crying, tremor, hypertonicity, excessive sucking, disordered sleep, hyperthermia, mottling, and postnatal convulsions have been reported in neonates after intrauterine exposure to oral LIORESAL. Neonates with risk of intrauterine exposure to LIORESAL should be carefully monitored for the development of signs consistent with withdrawal. If clinical manifestations of withdrawal develop, non-pharmacologic measures should be considered (for instance, minimizing sensory or environmental stimulation, maintaining temperature stability, increasing the frequency of feeds). Initiation of pharmacotherapy may be considered in neonates with moderate to severe signs of withdrawal to prevent further complications (See WARNINGS, Pregnancy and Lactation).

Neurologic

Respiratory Depression

Baclofen has been associated with central nervous system (CNS) depression including sedation, somnolence, loss of consciousness as well as serious cases of respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment and the elderly are at higher risk of experiencing these severe adverse effects. Concomitant use of CNS depressants with baclofen is also a contributing factor.

Concomitant Use With Opioids

Concomitant use of opioids with LIORESAL potentiates the risk of respiratory depression, profound sedation, syncope, and death.

Patients who require concurrent treatment with opioids or other CNS depressants should be observed carefully for signs and symptoms of CNS depression, and the dose of baclofen or opioid should be reduced accordingly.

Driving and Operating Machinery

LIORESAL may be associated with adverse effects such as dizziness, sedation, somnolence and visual impairment (see ADVERSE REACTIONS) which may impair the patient's reaction. Patients experiencing these adverse reactions should be advised to refrain from driving or using machines. Patients should also be cautioned that the central nervous system effects of LIORESAL may be additive to those of alcohol and other CNS depressants.

Renal impairment:

After oral LIORESAL dosing, severe neurological outcomes and symptoms of overdose including clinical manifestations of toxic encephalopathy (e.g. confusion, hallucination, somnolence, depressed level of consciousness and coma) have been reported in patients with renal impairment. Patients with renal impairment should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (e.g. somnolence, lethargy) (see SYMPTOMS AND TREATMENT

OF OVERDOSAGE). Caution should be exercised while administering LIORESAL in patients with renal impairment because baclofen is primarily excreted unchanged through the kidneys. In patients dependent on dialysis, a particularly low dose of LIORESAL should be selected i.e. approximately 5 mg daily. Unscheduled hemodialysis may be considered a treatment option in cases of severe baclofen toxicity as hemodialysis has been reported to effectively remove baclofen from the body, alleviate clinical symptoms of overdose and shorten the recovery time in these patients.

End Stage Renal Failure: LIORESAL should be administered to end stage renal failure patients only if the expected benefits are considered acceptable, given potential risks.
Concomitant medications that may impact renal function: 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 (see PRECAUTIONS, Drug interactions).

Stroke:
LIORESAL has not significantly benefited patients with stroke. These patients have also shown poor tolerability to the drug.

Pregnancy and Lactation:
Safe use of LIORESAL during pregnancy or lactation has not been established. Baclofen crosses the placental barrier and passes into breast milk. High doses are associated with an increased incidence of abdominal hernias in the fetuses of rats and of ossification defects in those of rats and rabbits. Therefore, the drug should be administered to pregnant patients, or women of child-bearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Infants exposed to LIORESAL through maternal oral dosing during pregnancy are at risk of experiencing baclofen withdrawal at birth; identification of this condition may be confounded due to delayed appearance of withdrawal symptoms in this population.

Epilepsy:

Extreme caution should be exercised in patients with epilepsy or a history of convulsive disorders. In such patients, the clinical state and electroencephalogram should be monitored at regular intervals during therapy, as deterioration in seizure control and EEG has been reported occasionally in patients taking LIORESAL**.**

Psychiatric and Nervous System Disorders:

Patients suffering from psychiatric disorders such as psychosis, schizophrenia, or confusional states should be treated cautiously with LIORESAL and kept under close surveillance, since exacerbation of these conditions may occur with LIORESAL treatment.

Suicide and suicide-related events have been reported in patients treated with baclofen. In some cases, the patients had additional risk factors associated with an increased risk of suicide including history of suicidal behaviour, depression, alcohol/substance abuse and/or concomitant use of medications known to increase risk of suicide. Close supervision of patients 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 (see ADVERSE REACTIONS).

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 patients should be monitored for symptoms of baclofen misuse, abuse or dependence e.g. dose escalation, drug-seeking behavior, development of tolerance.

PRECAUTIONS

Use in Children:

Safe use of LIORESAL (baclofen) in children under age 12 has not been established and it is, therefore, not recommended for use in children.

Posture and balance:

LIORESAL should be used with caution where spasticity is utilized to sustain upright posture and balance in locomotion, or whenever spasticity is utilized to obtain increased function (see DOSAGE and ADMINISTRATION).

Hepatic Impairment:

No studies have been performed in patients with hepatic impairment receiving LIORESAL therapy. As baclofen does not undergo predominant hepatic metabolism, its pharmacokinetics is unlikely to be altered to a clinically significant level in patients with hepatic impairment.

However, patients with severe hepatic impairment should be treated with caution, as they are in general more sensitive to therapeutic effects/adverse effects of drugs.

In rare instances, elevated SGOT, alkaline phosphatase and glucose levels in the serum have been recorded when using oral baclofen.

Others:

Caution should also be used in treating the following populations: patients with peptic ulceration (or a history of); elderly patients with cerebrovascular disorders; and patients with respiratory impairment. **Regarding patients with renal failure, see WARNINGS, Impaired Renal function.**

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 DOSAGE and ADMINISTRATION).

Urinary disorders:

LIORESAL should be used with caution in patients with underlying bladder sphincter hypertonia, since acute retention of urine may occur.

Laboratory tests:

The following laboratory tests have been found to be abnormal in a few patients receiving LIORESAL: aspartate aminotransferase, blood alkaline phosphatase and blood sugar (all elevated). Therefore, in patients with liver diseases or diabetes mellitus, appropriate laboratory tests should be performed periodically in order to ensure that no drug-induced changes in these underlying diseases have occurred.

Drug Interactions:

Anesthetics

Anesthetic agents may potentiate the CNS effects of baclofen.

Antidepressants

The concomitant administration of baclofen and tricyclic antidepressants may potentiate the pharmacological effects of baclofen, resulting in pronounced muscular hypotonia. In addition, concomitant use of tricyclic antidepressants can cause sedation, drowsiness and potentiate the effects of LIORESAL resulting in pronounced muscular hypotonia.

Lithium

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

MAO inhibitors

The concurrent use of MAO inhibitors and LIORESAL may result in increased CNS-depressant effects; therefore, caution is advised and the dosage of one or both agents should be adjusted accordingly.

Antihypertensives

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

Levodopa/Dopa Decarboxylase (DDC) inhibitor (carbidopa)

In patients with Parkinson's disease receiving treatment with baclofen and levodopa (alone or in combination with a DDC inhibitor, carbidopa), there have been several reports of mental confusion, hallucinations, headache, 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.

Antidiabetic agents

Isolated cases of increased blood glucose concentrations have been reported with LIORESAL; dosage adjustments of antidiabetic agents (oral and insulin) may therefore be necessary with combined LIORESAL treatment.

Neuromuscular blocking agents

Caution should be exercised when administering LIORESAL and magnesium sulfate (or other neuromuscular blocking agents), since a synergistic effect may theoretically occur.

Agents reducing renal function

Drugs or medicinal products that can significantly impact renal function (ex: memantine, NSAIDS) may reduce baclofen excretion leading to toxic effects (see WARNINGS, Impaired Renal Function).

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), synthetic opiates, hypnotics, anxiolytics or alcohol (see WARNINGS, Driving and Operating Machinery). 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.

Lactation

LIORESAL is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug.

Infertility

There are no data available on the effect of baclofen on fertility in humans. Baclofen did not impair male or female fertility at non-maternally toxic doses in rats (see TERATOLOGY AND REPRODUCTION STUDIES).

ADVERSE REACTIONS

Adverse effects most frequently occur at the start of treatment (e.g. sedation, somnolence), particularly if the dosage is increased too rapidly, if large doses are administered, and in the elderly patient. However, these effects are often transient and can be alleviated or eliminated by decreasing the dosage; they are seldom severe enough to warrant withdrawal of the medication.

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

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

In elderly patients or those patients with cerebrovascular disorder or a history of psychiatric illness, more serious adverse reactions may occur, such as hallucinations and confusion.

Muscular hypotonia of a degree sufficient to make walking or movement difficult may occur, but is usually relieved by readjusting the dosage. For this purpose, the overall dose of LIORESAL may be reduced, or the daytime dose reduced and the evening dose increased.

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

Some of the CNS and genitourinary symptoms reported may be related to the underlying disease rather than to drug therapy.

Adverse reactions listed below are ranked 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).

The most common adverse reactions associated with LIORESAL (baclofen) are transient somnolence, sedation, dizziness, weakness and fatigue. Other adverse reactions reported were:

Nervous system disorders:

Common: Headache, insomnia, muscular weakness, tremor, ataxia, respiratory depression, euphoric mood, depression, confusional state, hallucinations, nightmare, myalgia, nystagmus, and dry mouth.

Rare: Excitement, paresthesia, tinnitus, slurred speech, coordination disorder, rigidity, dystonia, dysarthria, epileptic seizures, lowered convulsion threshold, and dysgeusia.

Not known: Completed suicide, suicide attempt, suicide ideation, drug misuse, drug abuse, drug dependence (see WARNINGS, Psychiatric and nervous system disorders).

Eye disorders:

Common: Accommodation disorders, visual impairment.

Rare: Blurred vision, strabismus, miosis, mydriasis, diplopia.

Cardiac disorders:

Common: Cardiac output decreased.

Rare: dyspnea, palpitation, chest pain, syncope.

Not known: Bradycardia.

Vascular disorders:

Common: Hypotension.

Gastrointestinal disorders:

Very common: Nausea.

Common: Constipation, gastrointestinal disorders, retching, vomiting, diarrhea.

Rare: Anorexia, abdominal pain, and positive test for occult blood in stool.

Hepatobiliary disorders:

Rare: Hepatic function abnormal.

Skin and subcutaneous tissue disorders:

Common: Instances of rash, hyperhidrosis, pruritus.

Not known: Urticaria.

Renal and urinary disorders:

Common: Pollakiuria, enuresis, dysuria.

Rare: Nocturia, hematuria, urinary retention.

Reproductive system and breast disorders:

Rare: Erectile dysfunction, inability to ejaculate.

General disorders and administration site conditions:

Common: Fatigue, ankle edema.

Very rare: Hypothermia.

Not known: Drug withdrawal syndrome*.

Investigation:

Not known: Blood glucose increased.

Other:

Weight gain, nasal congestion.

*Drug withdrawal syndrome including, irritability, high-pitched crying, tremor, hypertonicity, excessive sucking, disordered sleep, hyperthermia, mottling, and postnatal convulsions has also been reported after intra-uterine exposure to oral LIORESAL

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre

Signs and Symptoms:

Symptoms of overdosage are predominantly those of central nervous system depression and include somnolence, depressed level of consciousness, respiratory depression, coma, seizures, confusion, hallucination, agitation, abnormal electroencephalogram (burst suppression pattern and triphasic waves), accomodation disorder, impaired pupillary refexes, muscular hypotonia, myoclonus, hyporeflexia or areflexia, hypotension or hypertension, bradycardia, tachycardia or cardiac arrhythmia, hypothermia, peripheral vasodilatation, nausea, vomiting, diarrhea, increased salivation, elevated LDH, AST, alkaline phosphatase, blood glucose values, sleep apnea and rhabdomyolysis.

The signs and symptoms may be further aggravated by co-administration of a variety of other agents including alcohol, diazepam, and tricyclic antidepressants.

Treatment:

There is no specific antidote. Supportive measures and symptomatic treatment should be given for complications such as hypotension, hypertension, convulsions, gastrointestinal disturbances, and respiratory or cardiovascular depression.

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) 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. A high urinary output should be maintained since LIORESAL (baclofen) is excreted mainly by the kidneys. For this purpose, generous quantities of fluid should be administered, possibly together with a diuretic. Hemodialysis (sometimes unscheduled) is indicated in severe poisoning associated with renal failure (see WARNINGS, Impaired Renal Function). In the event of convulsions, administer diazepam i.v. with caution.

DOSAGE AND ADMINISTRATION

The determination of optimal dosage of LIORESAL (baclofen) requires individual titration. Start therapy at a low dosage and increase gradually until optimum effect is achieved (usually between 40-80 mg daily).

Treatment should be started with a dosage of 15 mg daily, preferably in divided doses.

The following dosage titration schedule is suggested:

5 mg t.i.d. for 3 days
10 mg t.i.d. for 3 days
15 mg t.i.d. for 3 days
20 mg t.i.d. for 3 days

Thereafter additional increases may be necessary but the total daily dose should not exceed a maximum of 80 mg daily (20 mg q.i.d.).

The lowest dose compatible with an optimal response is recommended. If benefits are not evident after a reasonable trial period, patients should be slowly withdrawn from the drug (See WARNINGS).

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 WARNINGS).

Special populations

Renal impairment:

Because LIORESAL is primarily excreted unchanged through the kidneys, it should be given with caution in patients with renal insufficiency, and generally with a reduced dose. In patients dependent on dialysis, a particularly low dose of LIORESAL should be selected i.e. approximately 5 mg daily (see WARNINGS, Impaired Renal Function).

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 (see WARNINGS, Renal Impairment).

Since unwanted effects are more likely to occur in elderly patients or in patients with spastic states of cerebral origin, it is recommended that a very cautious dosage schedule be adopted in such cases and that the patient should be kept under appropriate surveillance. Patients should be monitored for signs of overdose, central nervous system depression and toxic encephalopathy such as drowsiness, impairment of consciousness, coma, respiratory depression, hallucinations, agitation, and convulsions (see **SYMPTOMS AND TREATMENT OF OVERDOSAGE**).

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 CLINICAL PHARMACOLOGY). However, LIORESAL has the potential of elevating liver enzymes. LIORESAL should be prescribed with caution in patients with hepatic impairment, although no dosage adjustment is needed (see PRECAUTIONS, Hepatic Impairment).

Geriatrics (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.

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.

AVAILABILITY

LIORESAL 10mg tablet: White to off-white, oval, flat-faced, bevel-edged tablets. Engraved GEIGY on one side and bisected with KJ on the other side.

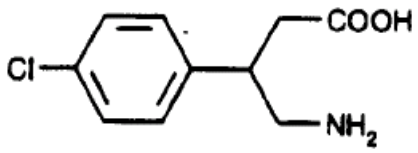
LIORESAL D.S. 20mg tablet: White to off-white, capsule-shaped tablets. Engraved GEIGY on one side and bisected with GW on the other side.

Available in bottles of 100 tablets.

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

CHEMISTRY AND PHARMACOLOGY

LIORESAL (baclofen) is 4-amino-3-(p-chlorophenyl) butyric acid and has the following structural formula:



Baclofen is a white to off-white, odorless or practically odorless crystalline powder, with a molecular weight of 213.67. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform.

Baclofen exerted a pronounced muscle-relaxant effect in the non-anesthetized mouse, rabbit, cat, and dog. Doses of up to 10 mg/kg p.o. did not affect coordination in mice. Intravenous doses of 1 or 2 mg/kg decreased polysynaptic (flexor) spinal reflexes in anesthetized rabbits or cats respectively by 50%. A similar reduction was found in decerebrated or spinal cats. The monosynaptic (extensor) spinal reflex was reduced 50% by a dose of 0.5 mg/kg i.v. in spinalized, decerebrate, or anesthetized cats. Baclofen had no direct effect on the alpha-motor nerve fibres, neuromuscular transmission, or contraction of extrafusal muscle fibres in anesthetized cats. An intravenous dose of 0.8 mg/kg diminished the tonic activity of gamma motoneurons in decerebrate cats by 50%. Baclofen diminished or abolished decerebrate rigidity in cats in doses of 1-3 mg/kg. It had no effect on the de-efferented muscle spindle or the slowly-adapting pulmonary stretch receptors in anesthetized cats.

Baclofen had anticonvulsive effects against thiosemicarbazide and pentetrazole-induced convulsions in mice but had no effect against electroshock or strychnine-induced convulsions.

An intravenous dose of 3-6 mg/kg exerted a hypnotic effect in the unanesthetized dog.

Large doses impaired respiration in mice, rabbits, and dogs. Doses of 1 mg/kg i.v. produced a fall in the blood pressure of anesthetized rabbits or cats, but 3 mg/kg i.v. had no effect on the blood pressure, heart rate, ECG, or respiration of unanesthetized dogs.

In man a single oral dose of 10 mg of baclofen is rapidly and almost completely absorbed whereas absorption of 20 mg and 40 mg doses is less complete. Animal studies indicate rapid distribution throughout the body except to the CNS where concentrations are lower than average. The decay in CNS concentration is, however, slower than the decay from other tissues.

About 85% of a single oral dose is excreted unchanged in the urine. The remaining 15% is mainly deaminated to β-(p-chlorophenyl)- γ-hydroxybutyric acid within 24 hours. LIORESAL is about 30% bound to serum proteins.

TOXICOLOGY

Acute Toxicity:

Species	Route	LD50 (mg/kg)
Mouse	i.v.	26 ± 6
Mouse	p.o.	75 ± 22
Rat	i.v.	112 ± 14
Rat	p.o.	150 ± 18
Rat	s.c.	137 ± 17

The toxic symptoms in mice and rats included ataxia, clonic-tonic convulsions and respiratory paralysis.

Species	Sex M	Sex F	No. of Groups	No. of Animals per Group	Dose mg/kg/day	Route	Dura-tion of Study	Toxic Effects
Rat	20	20	4	5M 5F	0,5,10; 20-80 (weekly increases of 10 mg/kg/day)	p.o.	30 D	Slight adrenal enlargement
Rat	10	10	5	2M 2F	Baclofen + diazepam: 0 + 0, 4 + 2, 20 + 10, 0 + 10, 20 + 0	p.o.	30 D	None
Dog	8	8	4	2M 2F	0,1,2, 4-8 (doubled in last week)	p.o.	30 D	Emesis at all dose levels, anorexia, salivation, ataxia, sedation, weight loss

Species	Sex M	Sex F	No. of Groups	No. of Animals per Group	Dose mg/kg/day	Route	Dura-tion of Study	Toxic Effects
Rat	80	80	4	20M 20F	0,5, 20-160, 40-500	p.o.	1 Y	Weight loss, mild alopecia, urinary incontinence at intermediate and high doses. Elevated mean neutrophil/ lymphocyte ratios and SGPT at intermediate and high doses.
Rat	280	28 0	1 3	Control: 100M 100F Test: 60M 60F	0,5, 25-50, 50-100	p.o.	1 Y	Reduced weight gain. Dose-related urinary frequency. Dose-related increase in incidence of ovarian cysts.
Dog	12	12	4	3M 3F	0, 2-4, 3-8, 4-12	p.o.	1 Y	Transient emesis, sedation, convulsions and cardiovascular collapse (single animal), possible slight adrenal enlargement, hind limb weakness or paralysis.

TERATOLOGY AND REPRODUCTION STUDIES

Reproductive toxicity

Oral baclofen showed no significant adverse effects on fertility or postnatal development at non-maternally toxic dose levels in rats (approximately 2.1-times the maximum oral mg/kg dose in adults). At maternally toxic dose levels (8.3-times the maximum oral mg/kg dose in adults), baclofen increased the the incidence of omphalocoeles (ventral hernias) in rats, an effect not seen in mice or rabbits. Delayed fetal growth (ossification of bones) in the fetuses of rats and rabbits was also observed at maternotoxic doses.

Rat: Doses of 4.4-5 and 17.7-21.3 mg/kg/day were administered orally to two groups of female rats during pre-mating, mating, gestation, and lactation. The only significant effect was a reduction in litter size and survivability of offspring (possibly due to agalactia) in the high-dose group. In another rat study, doses of 5 and 10 mg/kg/day were administered by gavage during the last trimester of pregnancy and throughout the lactation period. Five of 31 dams in the high-dose group showed severe weight loss from days 15-21 of gestation as well as agalactia and the entire litter of

each of these dams died by day 2 post-partum. In a third study, baclofen doses of 30 mg/kg/day produced symptoms of ataxia and drowsiness in dams and the death of 4 of 24 dams dosed from gestation Days 1 to 12. At this high dose level, there was a slight increase in the resorption rate; however, the number and size of the fetuses remained normal and no malformations were reported.

Rat and Mouse: Doses of 5 and 20 mg/kg/day were administered by gavage to two groups of pregnant rats on days 6-15 of gestation. The only significant finding was the presence of abdominal hernias in 4/160 fetuses in the high-dose group. In a second similar study, 1/229 control fetuses and 6/293 fetuses from dams receiving 20 mg/kg/day had abdominal hernias. Comparable lesions did not occur in a similar mouse study.

The average number of stillbirths or viable newborns did not differ significantly between control and medicated groups. The average weight of neonates from the high-dose group was significantly reduced.

Rabbit: Doses of 1, 5, and 10 mg/kg/day were administered by gavage to groups of rabbits from the 6th to 18th day of gestation. There was an increased incidence of unossified phalangeal nuclei of forelimbs and hind-limbs in the fetuses from the high-dose group. In another study, a slight increase in resorption rates and the number of rabbits that were non-gravid was observed in rabbits receiving 10 and 15 mg/kg/day of oral baclofen.

Mutagenicity and Carcinogenicity

Baclofen was negative for mutagenic and genotoxic potential in tests in bacteria, mammalian cells, yeast, and Chinese hamsters.

A 2-year rat study (oral administration of baclofen) found no evidence of carcinogenesis. 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. The clinical relevance of these findings is not known.

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PART III: CONSUMER INFORMATION

PrLIORESAL®
Baclofen Tablets

This leaflet is part III of a three-part -"Product Monograph" published when LIORESAL® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about LIORESAL®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

LIORESAL is used to reduce and relieve the excessive stiffness and/or spasms in your muscles occurring in various conditions such as multiple sclerosis and diseases or injuries of the spinal cord.

What it does:

Due to the relaxation of muscle and the consequent relief from pain, LIORESAL improves your ability to move, makes it easier for you to manage your daily activities and facilitates physiotherapy.

If you have any questions about how LIORESAL works or why this medicine has been prescribed for you, ask your doctor.

When it should not be used:

Do not take LIORESAL:

- If you are allergic (hypersensitive) to baclofen or any of the other ingredients listed in "**What the nonmedicinal ingredients are**".

If this applies to you, tell your doctor without taking LIORESAL.

If you think you may be allergic, ask your doctor for advice.

What the medicinal ingredient is:

The active substance of LIORESAL is baclofen.

What the non-medicinal ingredients are:

The non-medicinal ingredients are: microcrystalline cellulose, cornstarch, magnesium stearate and povidone.

What dosage forms it comes in:

LIORESAL is available in 10 mg and 20 mg tablets.

WARNINGS AND PRECAUTIONS

SERIOUS WARNINGS AND PRECAUTIONS

Taking LIORESAL with opioid medicines, alcohol, or other central nervous system depressants (including street drugs) can cause severe drowsiness, decreased awareness, breathing problems, coma, and death.

BEFORE you use LIORESAL talk to your doctor or pharmacist if you:

- Have kidney disease. Your doctor will decide whether or not LIORESAL is the appropriate treatment for you;
- Are suffering from epilepsy (seizures);
- Have acute pain in your stomach (ulcer) or intestines, breathing problems, liver disease, or a disturbance of blood circulation in your brain;
- Are taking medicines for arthritis or pain (see section: "**Interactions with this medication**");
- Have difficulty urinating;
- Have Parkinson's disease or certain mental illnesses accompanied by confusion or depression;
- Are diabetic;
- Have or had thoughts of harming or killing yourself, have or had depression, have a history of alcoholism or drink alcohol to excess, have a history of drug abuse and dependence, or are taking medicines associated with increased suicide risk;
- Have thoughts of harming or killing yourself at any time, speak to your doctor straightaway or go to a hospital. Also, ask a relative or close friend to tell you if they are worried about any changes in your behavior and ask them to read this leaflet.

Older people (aged 65 years or above) or people with a disturbance of circulation in the brain

If you are in one of these groups, you may experience more side effects. Therefore, your doctor will keep you under appropriate surveillance and may adapt the dose of LIORESAL you take.

Children and adolescents

Safe use of LIORESAL in children under age 12 has not been established and it is therefore not recommended for use in children.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine.

You should not use LIORESAL during pregnancy unless your doctor advises you to do so. Tell your doctor if you are pregnant, planning to become pregnant, or breast-feeding. He or she will discuss with you the potential risk of taking LIORESAL during pregnancy or if you are breast-feeding. Use of LIORESAL during pregnancy may result in the newborn experiencing withdrawal from the drug including, irritability, high-pitched crying,

trembling, increased muscle tone, excessive sucking, disordered sleep, increase in body temperature, uneven discolored patches on the skin, and convulsions and other symptoms related to sudden stop of treatment sometime after delivery. Your doctor may need to treat your newborn for withdrawal reactions.

Driving and using machines

In some people, LIORESAL may be associated with dizziness, sleepiness or visual disturbance. If this happens to you, do not drive a car, use a machine, or do other things that need your full attention.

Further safety measures

Before having any kind of surgery (including by the dentist), or emergency treatment, tell the doctor in charge that you are taking LIORESAL.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with LIORESAL include:

- Alcohol;
- Sedative drugs;
- Medicines used to treat mood disorders such as antidepressants and lithium;
- Medicines used to treat high blood pressure;
- Medicines used to treat Parkinson's disease;
- Medicines for arthritis or pain.

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not drink alcohol during your treatment with LIORESAL.

PROPER USE OF THIS MEDICATION

Usual dose:

Follow your doctor’s instructions carefully. Do not exceed the recommended dose.

How much LIORESAL to take

Treatment usually starts with 15 mg daily, preferably taken in divided doses. The dose is then gradually increased until the best results are obtained; this may be between 40 mg to 80 mg per day, taken in divided doses.

The dose prescribed by your doctor may be different from that written here. If this is the case, follow the doctor's instructions.

Your doctor will tell you exactly how many tablets of LIORESAL to take.

Depending on how you respond to the treatment, your doctor may suggest a higher or lower dose.

When to take LIORESAL

Taking LIORESAL at the same time each day will help you to remember when to take your medicine.

How to take LIORESAL

Be sure to take this medicine regularly, and exactly as your doctor tells you. This will help you to get the best results and reduce the risk of side effects.

How long to take LIORESAL

Continue taking LIORESAL as your doctor tells you.

If you have questions about how long to take LIORESAL, talk to your doctor or your pharmacist.

Do not suddenly stop taking LIORESAL without first checking with your doctor. He or she will tell you when and how you can stop taking this medicine; stopping suddenly can make your condition worse.

If you stop your treatment suddenly, you may experience: nervousness, feeling confused, hallucinations, abnormal thinking or behaviour, convulsions, uncontrollable twitching, jerking or writhing movements, fast heart beat, high body temperature. The excessive stiffness (spasms) in your muscles may also worsen.

Overdose:

If you have accidentally taken many more tablets than your doctor has prescribed, seek immediate emergency medical treatment, even though you do not feel sick.

The main symptoms of overdose are drowsiness, breathing difficulties, trouble of consciousness and being unconscious (coma).

Other symptoms may include: feeling confused, hallucinations, agitation, convulsions, blurred vision, unusual muscle weakness, sudden contraction of the muscles, poor or absent reflexes, high or low blood pressure, slow, fast or irregular heart beat, low body temperature, nausea, vomiting, diarrhea or excessive salivation, trouble breathing during sleep (sleep apnoea), pain in muscles, fever and dark urine (rhabdomyolysis).

If you have **kidney disease** and have accidentally taken more tablets or more syrup than **your doctor** has prescribed, you may experience neurological symptoms of overdose (e.g. drowsiness, feeling confused, hallucinations).

Missed Dose:

If you have forgotten to take one of your scheduled doses, take it as soon as you remember. However, if it is almost time for your next dose, do not take the missed one at the same time as the scheduled one, otherwise you will be doubling the dose. Just go back to your regular dosing timetable. If you have forgotten to take several doses you should contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, LIORESAL can have some side effects, although not everybody gets them. These are often mild and are usually at the start of treatment; they normally wear off after a few days.

Very common side effects
These side effects may affect more than 1 in 10 patients:

- Drowsiness, sleepiness;
- Nausea.

If any of these affects you severely, **tell your doctor.**

Common side effects
These side effects may affect between 1 and 10 in every 100 patients:

- Feeling faint, tiredness, dizziness, headache, inability to sleep, weakness in arms and legs, pain in muscles, uncontrollable eye movements, dry mouth;
- Disturbance of the digestive tract, retching, vomiting, constipation, diarrhea;
- Sweating a lot;
- Passing more urine than normal, bedwetting.

If any of these affects you severely, **tell your doctor.**

Rare side effects
These side effects may affect between 1 and 10 in every 10,000 patients:

- Tingling or numbness of the hands and/or feet, difficulty in speaking, taste disturbance;
- Abdominal pain;
- Sudden decrease in urine;
- Inability to get or to maintain an erection (impotence).

Side effect also reported (frequency unknown)
- Increased blood sugar;
- Drug misuse, drug abuse, drug dependence.

If any of these affects you severely, **tell your doctor.**

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical treatment
		Only if severe	In all cases	
Common	Breathing problems		√	
	Feeling of confusion		√	
	Feeling of extreme happiness		√	
	Sad mood (depression)		√	
	Loss of coordination affecting balance and walking, limb and eye movements and/or speech (signs of ataxia)		√	
	Trembling		√	
	Hallucinations		√	
	Nightmares		√	
	Blurred vision/visual disturbance		√	
	Shortness of breath at rest or with activity, swelling in the legs and tiredness (signs of decreased cardiac output)		√	
	Low blood pressure (hypotension)		√	
	Skin rash and hives		√	
	Difficulty passing urine, pain when passing urine or a sudden decrease in urine		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical treatment
		Only if severe	In all cases	
Rare	Abdominal pain, yellowing of the skin or eyes and tiredness (signs of liver disturbance)			√
	Convulsions			√
Very rare	Low body temperature		√	
Not known	Symptoms following sudden discontinuation of the medicine (drug withdrawal syndrome)		√	
	Slow heart beat		√	
	Suicidal Behavior: thoughts or actions about harming or killing yourself		√	

This is not a complete list of side effects. For any unexpected effects while taking LIORESAL, contact your doctor or pharmacist.

HOW TO STORE IT

- Do not use after the expiry date shown on the bottle.
- Protect from heat and humidity.
- Keep out of the reach and sight of children.

You can report any suspected adverse reactions associated with the use of health products to Health Canada by :

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax;
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you want information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Please consult your doctor or pharmacist with any questions or concerns you may have regarding your individual condition.

This document plus the full product monograph, prepared for health professionals can be found at:

www.novartis.ca

or by contacting the sponsor, Novartis Pharmaceuticals Canada Inc., at:

1-800-363-8883

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