PRODUCT MONOGRAPH

PrLIORESAL® Intrathecal

(baclofen injection)

0.05 mg/mL, 0.5 mg/mL and 2 mg/mL

For intrathecal injection and infusion only

Antispastic Agent

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THERAPEUTIC CLASSIFICATION

Antispastic Agent

CLINICAL PHARMACOLOGY

The precise mechanisms of action of LIORESAL (baclofen) as an antispastic agent are not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflex transmission at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals. Actions at supraspinal sites may also contribute to its clinical effect. Baclofen is an analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and may exert its effects by stimulation of the $GABA_B$ receptor subtype.

Baclofen has been shown to have general Central Nervous System (CNS) depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia and respiratory and cardiovascular depression. A dose-dependent inhibitory effect on erectile function has been shown in men through $GABA_B$ receptor stimulation.

In neurological diseases associated with spasm of the skeletal muscles, LIORESAL Intrathecal may have beneficial action on reflex muscle contractions, painful spasm, automatism, hyperreflexia, trismus and clonus. Neuromuscular transmission is not affected by baclofen. Baclofen may also reduce pain associated with spasticity.

Pharmacodynamics of LIORESAL Intrathecal:

Intrathecal Bolus:

The onset of action is generally half an hour to one hour after administration of an intrathecal bolus dose. Peak antispastic effect is seen at approximately 4 hours after dosing and effects may last 4 to 8 hours. Onset, peak response, and duration of action vary with individual patients depending on the dose and severity of symptoms.

Continuous Intrathecal Infusion:

The antispastic action is first seen at 6 to 8 hours after initiation of continuous infusion. Maximum efficacy is observed in 24 to 48 hours.

Pharmacokinetics of LIORESAL Intrathecal:

After LIORESAL Intrathecal administration, the concentration of baclofen in the Cerebrospinal Fluid (CSF) is approximately 100 times higher than what is found following oral administration.

Because of slow CSF circulation and a baclofen concentration gradient from the lumbar to the cisternal CSF, the pharmacokinetic parameters as described below should be interpreted considering a high inter- and intra-patient variability.

The clearance of intrathecal baclofen, calculated from intrathecal bolus or continuous infusion studies, approximate its CSF turnover, suggesting elimination via bulk-flow removal of CSF. Direct infusion into the spinal subarachnoid space bypasses absorption processes and allows exposure to the receptor sites in the dorsal horn of the spinal cord.

Intrathecal bolus:

After a bolus lumbar injection of 50 or 100 μg LIORESAL Intrathecal in 7 patients, the average CSF elimination half-life was 1.51 hours over the first four hours and the average CSF clearance was approximately 30 mL/hour. After single intrathecal bolus injection/short-term infusion, the

volume of distribution in intrathecal compartment, calculated from CSF levels, ranges from 22 to 157 mL.

Continuous infusion:

A study, conducted in 10 patients, suggests that the mean CSF clearance for continuous intrathecal infusion of LIORESAL is approximately 30 mL/hour.

Continuous intrathecal infusion daily doses of 50 to 1200 µg result in lumbar CSF concentrations of baclofen as high as 130 to 1240 ng/mL at steady state. According to the half-life measured in the CSF, CSF steady state concentrations will be reached within 1-2 days. During Intrathecal infusion the plasma concentrations do not exceed 5 ng/mL.

Limited pharmacokinetic data suggest that a lumbar-cisternal baclofen concentration gradient of about 4:1 is established during continuous baclofen infusion. This is based upon simultaneous CSF sampling via cisternal and lumbar tap during continuous baclofen infusion at the lumbar level in doses associated with therapeutic efficacy. The interpatient variability was considerable. This gradient suggests that spasticity in the lower extremities may be relieved with little effect on the upper limbs and with fewer cerebral adverse reactions due to diminished effects on the brain.

Special populations:

Geriatrics

No pharmacokinetic data is available in elderly patients after administration of LIORESAL Intrathecal. When a single dose of the oral formulation is administered, data suggest that elderly patients have a slower rate of absorption and elimination, a slightly prolonged elimination half-life, but a similar systemic exposure to baclofen compared to young adults.

Hepatic impairment

No pharmacokinetic data is available in patients with hepatic impairment after administration of LIORESAL Intrathecal. However, as the liver does not play a significant role in the disposition

of baclofen it is unlikely that its pharmacokinetics would be altered to a clinically significant level in patient with hepatic impairment.

Renal impairment

No pharmacokinetic data is available in patients with renal impairment after administration of LIORESAL Intrathecal. Since baclofen is primarily eliminated unchanged through the kidneys, accumulation of unchanged drug in patients with renal impairment cannot be excluded. Severe neurological outcomes have been reported in patients with renal impairment after oral administration, thus LIORESAL Intrathecal should be given with special care and caution in these patients (see PRECAUTIONS, Renal Impairment).

INDICATIONS AND CLINICAL USE

LIORESAL Intrathecal (baclofen injection) is indicated for the management of patients with severe spasticity due to spinal cord injury or multiple sclerosis who are unresponsive to oral baclofen or who experience unacceptable side effects at effective oral doses.

LIORESAL Intrathecal therapy may be considered as an alternative to destructive neurosurgical procedures.

Prior to implantation of a device for chronic intrathecal infusion, patients must demonstrate a positive clinical response to a LIORESAL Intrathecal screening trial (see DOSAGE AND ADMINISTRATION).

LIORESAL Intrathecal has been used in patients with other spasticity of cerebral origin, e.g. spasticity following hypoxic encephalopathy, head injury, or stroke; however, clinical experience is limited.

CONTRAINDICATIONS

Known or suspected hypersensitivity to baclofen or to any of the excipients.

LIORESAL Intrathecal should not be administered by intravenous, intramuscular, subcutaneous or epidural routes.

WARNINGS

Because of the possibility of potential life-threatening CNS depression, cardiovascular collapse and/or respiratory failure, physicians must be adequately trained in intrathecal infusion therapy.

Specific instructions for programming and/or refilling the implantable pump are given by the pump manufacturers, and must be strictly adhered to. Consult pump manufacturer's literature for information on the appropriate use and care of these devices.

Because of the risks associated with the screening procedure and the adjustment of dosage following pump implantation, these procedures must be conducted in a medically supervised and adequately equipped environment (see DOSAGE AND ADMINISTRATION).

Resuscitative equipment should be available.
The pump system should not be implanted until the patient's response to bolus intrathecal injection of LIORESAL Intrathecal (baclofen injection) has been properly evaluated and found to be clinically safe and effective.

Following surgical implantation of the pump, particularly during the initial phase of pump use the patient should be monitored closely until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

Whenever the dosing rate of the pump and/or the concentration of LIORESAL Intrathecal in the reservoir is adjusted, close medical monitoring is required until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

It is mandatory that the patient and all those involved in the care of the patient receive adequate information regarding the risks of LIORESAL Intrathecal treatment. All medical personnel and care givers should be instructed in 1) the signs and symptoms of overdose, 2) procedures to be followed in the event of overdose and 3) proper home care of the pump and insertion site.

Inflammatory mass at the tip of implanted catheter with LIORESAL Intrathecal

Cases of inflammatory mass at the tip of the implanted catheter have been reported in patients receiving LIORESAL Intrathecal monotherapy. The most frequent symptom associated with these masses is decreased therapeutic response (worsening spasticity, return of spasticity when previously well controlled, withdrawal symptoms, poor response to escalating doses, or frequent or large dosage increases). It is known that inflammatory mass at intrathecal tip can result in pain and serious neurological impairment. Clinicians should monitor patients on LIORESAL Intrathecal therapy carefully for any new neurological signs or symptoms. In patients with new neurological signs or symptoms suggestive of an inflammatory mass, consider a neurosurgical consultation since many of the symptoms of inflammatory mass are similar to the symptoms experienced by patients with severe spasticity from their disease. A diagnostic imaging procedure may be appropriate to confirm or rule-out inflammatory mass. Inflammatory masses have also been reported in patients receiving pharmacy compounded drugs or admixtures, including opioids. Diagnosis and management of inflammatory mass in these patients should take into consideration the pharmacology of the drugs in addition to LIORESAL.

Scoliosis

The onset of scoliosis or worsening of a pre-existing scoliosis has been reported in patients treated with LIORESAL Intrathecal. Signs of scoliosis should be monitored during treatment with LIORESAL Intrathecal.

<u>Abrupt Drug Withdrawal</u>:

Abrupt discontinuation of LIORESAL Intrathecal, regardless of the cause, has resulted in sequelae that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure and death.

Prevention of abrupt discontinuation of LIORESAL Intrathecal requires careful attention to proper programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of LIORESAL withdrawal. Special attention should be given to patients at apparent risk (e.g. spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or LIORESAL Intrathecal). Consult the technical manual of the implantable infusion system for additional postimplant clinician and patient information. (see WARNINGS).

In the first 9 years of post-marketing experience, 27 cases of withdrawal temporally related to the cessation of LIORESAL Intrathecal therapy were reported; six patients died. In most cases, symptoms of withdrawal appeared within hours to a few days following interruption of LIORESAL Intrathecal therapy. Common reasons for abrupt interruption of LIORESAL Intrathecal therapy included malfunction of the catheter (especially disconnection), low volume in the pump reservoir, device malfunction and end of pump battery life; human error may have played a causal or contributing role in some cases. Device malfunction resulting in altered drug delivery leading to withdrawal symptoms including death has been reported.

All patients receiving LIORESAL Intrathecal therapy are potentially at risk for withdrawal. Early symptoms of baclofen withdrawal may include return of baseline spasticity, pruritus, hypotension, paresthesias and priapism (prolonged and potentially painful erections requiring immediate medical attention). Some clinical characteristics of the advanced LIORESAL Intrathecal withdrawal syndrome may resemble autonomic dysreflexia, infection (sepsis), malignant hyperthermia, neuroleptic-malignant syndrome, or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis.

Rapid, accurate diagnosis and treatment in an emergency room or intensive care setting are important in order to prevent the potentially life-threatening central nervous system and systemic effects of LIORESAL Intrathecal withdrawal. The suggested treatment for LIORESAL Intrathecal withdrawal is the restoration of LIORESAL Intrathecal at or near the same dosage as before therapy was interrupted. However, if restoration of intrathecal delivery is delayed, treatment with GABA-ergic agonist drugs such as oral baclofen, or oral, enteral, or intravenous benzodiazepines may prevent potentially fatal sequelae. Oral baclofen alone should not be relied upon to halt the progression of the effects of LIORESAL Intrathecal withdrawal.

Seizures have been reported during overdose and with withdrawal from LIORESAL Intrathecal as well as in patients maintained on therapeutic doses of LIORESAL Intrathecal.

Therefore, except for serious adverse reactions and overdose related emergencies, the dose should always be reduced slowly when the drug is discontinued (over a period of approximately 1-2 weeks).

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 PRECAUTIONS, Pregnant Women).

PRECAUTIONS

Screening:

Patients should be infection free prior to the screening trial with LIORESAL Intrathecal (baclofen injection) because the presence of a systemic infection may interfere with an assessment of the patient's response to bolus intrathecal baclofen.

Careful monitoring of respiratory and cardiovascular functions is essential during initial test dose administration (screening phase), especially in patients with cardiopulmonary disease and respiratory muscle weakness as well as those being treated concomitantly with benzodiazepine-type preparations or opiates who are at higher risk of respiratory depression.

Pump implantation:

Patients should be infection free prior to pump implantation because the presence of infection may increase the risk of surgical complications. Moreover, a systemic infection may complicate attempts to adjust the dose.

Patient monitoring:

Following surgical implantation of the pump, particularly during the initial phases of pump use, and on each occasion that the dosing rate of the pump and/or the concentration of baclofen in the reservoir is adjusted, the patient should be monitored closely until it is certain that the patient's response to the infusion is acceptable and stable.

Pump adjustment and titration:

In most patients, it will be necessary to increase the dose gradually over time to maintain effectiveness; a sudden requirement for substantial dose escalation typically indicates a catheter complication (i.e., catheter kink or dislodgement).

Reservoir Filling:

Reservoir refilling must be performed by fully trained and qualified personnel following the directions provided by the pump manufacturer. Refill intervals should be carefully calculated to prevent depletion of the reservoir, as this would result in the return of severe spasticity and possibly symptoms of withdrawal. Depending on individual daily dose requirements and the flow rate of the pump, refill intervals generally vary between one and three months.

Strictly aseptic filling is required to avoid microbial contamination and serious infection. A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir.

Extreme caution must be used when filling an implantable pump equipped with an injection port that allows direct access to the intrathecal catheter. Direct injection into the catheter through the access port may cause a life-threatening overdose.

In order to prevent excessive weakness and falling, LIORESAL Intrathecal 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 and possibly prevent the formation of deep vein thrombosis.

An attempt should be made to discontinue concomitant oral antispastic medication to avoid possible overdose or adverse drug interactions, preferably before initiating baclofen infusion, with careful monitoring by the physician. However, abrupt reduction or discontinuation of concomitant antispastics during chronic intrathecal therapy with baclofen should be avoided.

<u>Driving and Operating Machinery:</u>

Central nervous systems (CNS) depressant effects, such as somnolence and sedation have been reported in some patients on intrathecal baclofen. Other listed events include ataxia, hallucinations, diplopia and withdrawal symptoms (see ADVERSE REACTIONS). Patients should be cautioned regarding the operation of automobiles or dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system effects of baclofen may be additive to those of alcohol and other CNS depressants.

Geriatrics:

Elderly patients may be more susceptible to the side effects of oral baclofen in the titration stage and this may also apply to intrathecal baclofen.

Pediatrics:

The safety and efficacy of LIORESAL Intrathecal has not been studied in patients under 18 years of age. Its use in pediatric patients is not recommended unless the benefits outweigh the risk.

Pregnant Women:

There are no adequate and well-controlled studies of LIORESAL Intrathecal in pregnant women. LIORESAL Intrathecal has been detected in maternal plasma (see CLINICAL PHARMACOLOGY) and is known to cross the placental barrier (see TOXICOLOGY). Post-marketing reports on mothers who used LIORESAL Intrathecal during pregnancy suggest a higher than expected rate of preterm delivery and delivery by caesarian section. Further, these preterm births have resulted in low birth weights according to what would be expected for gestational age. Therefore, LIORESAL Intrathecal should not be used during pregnancy unless the potential benefits to the mother outweigh the potential risk to the fetus.

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.

Nursing Women:

Oral baclofen at therapeutic doses passes into breast milk. LIORESAL Intrathecal should not be used in nursing women unless the potential the benefit outweigh the risk.

Patients with Special Diseases and Conditions:

In patients with abnormal CSF flow, the spread of the drug and therefore, the distribution of antispastic activity may be inadequate.

Patients suffering from psychotic disorders, schizophrenia, confusional states, or Parkinson's disease should be treated cautiously with LIORESAL Intrathecal and kept under careful surveillance as exacerbations of these conditions have been observed with oral baclofen administration.

Close supervision of patients should accompany therapy with LIORESAL Intrathecal. 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. Suicide and suicide-related events have been reported in patients treated with intrathecal baclofen (see ADVERSE REACTIONS).

Special attention should be given to patients known to suffer from epilepsy as seizures have been reported during overdose with, and withdrawal from, LIORESAL Intrathecal, as well as in patients maintained on therapeutic doses of LIORESAL Intrathecal.

LIORESAL Intrathecal should be used with caution in patients with a history of autonomic dysreflexia. The presence of nociceptive stimuli or abrupt withdrawal of LIORESAL Intrathecal may cause an autonomic dysreflexic episode.

LIORESAL should be used with caution in patients with cerebrovascular or respiratory insufficiency, as these conditions may be exacerbated by baclofen.

Interaction of intrathecal baclofen with underlying, non-CNS related diseases is unlikely because the systemic availability of the drug after intrathecal administration is substantially lower than after oral administration. Nevertheless, observations after oral baclofen therapy suggest that caution should be exercised in the following situations: history of peptic ulcers, pre-existing sphincter hypertonia, and impaired hepatic function.

Renal impairment:

No studies have been performed in patients with renal impairment receiving LIORESAL Intrathecal therapy. After oral LIORESAL dosing, severe neurological outcomes including clinical manifestations of toxic encephalopathy (e.g. somnolence, depressed level of consciousness and coma) have been reported in patients with renal impairment. Caution should be exercised while administering LIORESAL Intrathecal in patients with renal impairment because baclofen is primarily excreted unchanged through the kidneys. Patients with severe renal impairment should be treated with extra caution, as they are in general more sensitive to therapeutic effects/adverse effects of drugs. Severely renal impaired patients should be closely monitored for prompt diagnosis of early signs and/or symptoms of toxicity (see SYMPTOMS AND TREATMENT OF OVERDOSAGE).

Hepatic Impairment:

No studies have been performed in patients with hepatic impairment receiving LIORESAL Intrathecal 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, the 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.

Drug Interactions:

There is little experience with the use of LIORESAL Intrathecal in combination with systemic medications to predict specific drug-drug interactions, although it is suggested that the low baclofen systemic exposure observed after intrathecal administration could reduce the potential for pharmacokinetic interactions (see CLINICAL PHARMACOLOGY).

Drug-Drug Interactions

Levodopa/ Dopa Decarboxylase (DDC) inhibitor (carbidopa)

Concomitant use of oral LIORESAL and levodopa (alone or in combination with a DDC inhibitor, carbidopa) resulted in increased risk of adverse events such as visual hallucinations, confusional state, headache and nausea. Worsening of the symptoms of Parkinsonism has also been reported. Thus, similar interaction can be anticipated for intrathecal LIORESAL.

Anesthetics

Concomitant use of intrathecal baclofen and general anesthetics (e.g. fentanyl, propofol) may increase the risk of cardiac disturbances and seizures. Thus, caution should be exercised when anesthetics are administered to patients receiving intrathecal LIORESAL.

Morphine

The combined use of morphine and intrathecal baclofen was responsible for hypotension in one patient. The potential for this combination to cause dyspnea or other CNS symptoms cannot be excluded.

The co-administration of other intrathecal agents with LIORESAL Intrathecal has not been tested and the safety of these combinations is unknown.

Alcohol and other compounds affecting CNS

The central nervous system depressant effects of alcohol and other compounds affecting the CNS (e.g. analgesics, neuroleptics, barbiturates, benzodiazepines, anxiolytics) may be additive to the effects of LIORESAL Intrathecal. Increased sedation may occur when LIORESAL Intrathecal is taken concomitantly with other drugs causing CNS depression, including other muscle relaxants (such as tizanidine), synthetic opiates, hypnotics, anxiolytics or alcohol (see PRECAUTIONS - Driving and Operating Machinery). 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.

Tricyclic antidepressants

When using oral baclofen, concurrent treatment with tricyclic antidepressants may potentiate the effect of LIORESAL, 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. Therefore, caution is advised when using LIORESAL Intrathecal in this combination.

Lithium

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

Antihypertensives

Since concomitant treatment with oral LIORESAL and antihypertensives is likely to increase antihypertensive effects, it is recommended that blood pressure is checked and if necessary, the dosage of antihypertensive medication adjusted accordingly.

ADVERSE REACTIONS

Baclofen has been shown to have general CNS depressant properties, causing sedation, somnolence, and respiratory and cardiovascular depression.

The most commonly reported adverse events with LIORESAL Intrathecal (baclofen injection) in clinical trials were drowsiness, weakness in the lower extremities, dizziness and seizures.

Adverse drug reactions from clinical trials are listed in the table below according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked under headings of frequency, the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: 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.

Adverse events associated with the delivery system (e.g. mass at the tip of the catheter, catheter dislocation with possible complications, pocket infection, meningitis, overdose due to wrong manipulation of the device) have been reported, whereby in some cases a causal relationship with baclofen cannot be excluded (see Warnings). These are in addition to those listed below. Device malfunction resulting in altered drug delivery leading to withdrawal symptoms including death has been reported. In a fatal case of a child (causality with baclofen uncertain), inflammatory signs in the posterior horns and signs of arachnoiditis in proximity of the catheter tip were observed. This corresponds to observations in dogs, where chronic inflammatory reactions to the foreign body of the catheter were observed, independently of baclofen concentration.

Incidence of Most Frequent Adverse Events in US Clinical Trials

Adverse Event	Number of patients reporting events (%)		
	Screening (N= 244)	Titration (N= 214)	Maintenance (N=214)
Somnolence	13 (5.3%)	11(5.1%)	18 (8.4%)
Weakness, Lower Extremities	1 (0.4%)	11(5.1%)	15 (7.0%)
Dizziness	6 (2.4%)	5 (2.3%)	12(5.6%)
Convulsion	1 (0.4%)	4 (1.9%)	11 (5.1%)
Headache	0 (0%)	3 (1.4%)	9 (4.2%)
Nausea/Vomiting	3 (1.2%)	5 (2.3%)	3 (1.4%)
Numbness/Itching/Tingling	2 (0.8%)	1 (0.5%)	8 (3.7%)
Hypotension	3 (1.2%)	0 (0%)	5 (2.3%)
Vision Blurred	0 (0%)	2 (0.9%)	5 (2.3%)
Constipation	0 (0%)	2 (0.9%)	5 (2.3%)
Hypotonia	2 (0.8%)	3 (1.4%)	2 (0.9%)
Dysarthria	0 (0%)	1 (0.5%)	6 (2.8%)
Coma (Overdose)	0 (0%)	4 (1.9%)	3 (1.4%)
Lethargy	1 (0.4%)	0 (0%)	4 (1.9%)
Weakness, Upper Extremities	1 (0.4%)	0 (0%)	4 (1.9%)
Hypertension	1 (0.4%)	2 (0.9%)	2 (0.9%)
Dyspnea	1 (0.4%)	2 (0.9%)	1 (0.5%)

In addition to the more common adverse events reported above, the following adverse events were observed during clinical trials elsewhere or reported by clinicians.

Metabolism and nutritional disorders:

Uncommon: Dehydration, weight loss, albuminuria and hyperglycemia

Psychiatric disorders:

Common: Depression, anxiety, agitation

Uncommon: Suicide ideation and suicide attempt, hallucinations, paranoia, euphoric mood

Nervous system disorders:

Common: Confusional state, disorientation, insomnia, sedation, paresthesia, fatigue, lethargy

Uncommon: nystagmus, ataxia, memory impairment

Eye disorders:

Common: Accommodation disorder, diplopia

Cardiac disorders:

Uncommon: Bradycardia

Rare: pulmonary embolism

Vascular disorders:

Uncommon: Deep vein thrombosis, flushing, pallor

Gastrointestinal disorders:

Common: Dry mouth, diarrhea, decreased appetite, increased salivation

Uncommon: Ileus, hypogeusia, dysphagia

Respiratory, thoracic and mediastinal disorders:

Common: Respiratory depression, pneumonia

Renal and urinary disorders:

Common: urinary incontinence, urinary retention

Reproduction system and breast disorders:

Common: Sexual dysfunction

Skin and subcutaneous tissue disorders:

Common: Urticaria, pruritus, facial and/or peripheral edema

Uncommon: Alopecia, hyperhidrosis

Musculoskeletal and connective tissue disorders:

Common: Hypertonia

General disorders and administration site conditions:

Common: Asthenia, pyrexia, chills, pain

Uncommon: Hypothermia

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with LIORESAL Intrathecal via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Nervous system disorders: dysphoria

Respiratory, thoracic and mediastinal disorders: bradypnea

Musculoskeletal and connective tissue disorders: scoliosis (see WARNINGS)

Reproductive system and breast disorders: erectile dysfunction

SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre for the most current information.

Special attention must be given to recognizing the signs and symptoms of overdosage at all times, especially during the initial "screening" and "dose titration" phase of treatment and also during reintroduction of LIORESAL Intrathecal (baclofen injection) after a period of interruption of therapy.

Symptoms

Signs of overdose may appear suddenly or insidiously.

Less sudden and/or less severe forms of overdose may present with signs of drowsiness, lightheadedness, dizziness, somnolence, seizures, loss of consciousness, hypothermia, excessive salivation, nausea and/or vomiting and cephalad progression of hypotonia. Respiratory depression, apnea, and coma result from serious overdosage.

Serious overdose may occur, for example, by inadvertent delivery of catheter contents during catheter patency/position analysis. Errors in programming, excessively rapid dose increases, and concomitant treatment with oral baclofen are other possible causes of overdosage. Possible pump malfunction should also be investigated.

Symptoms of severe LIORESAL Intrathecal overdose (coma) were reported in a sensitive adult patient after receiving a 25 μg intrathecal bolus dose.

Treatment

There is no specific antidote for treating overdoses of intrathecal baclofen, however, the following steps should generally be undertaken:

1. Residual LIORESAL solution should be removed from the pump as soon as possible.

2. Patients with respiratory depression should be intubated if necessary, until the drug is eliminated.

If lumbar puncture is not contraindicated, consideration should be given in the early stage of the intoxication to withdrawing 30 to 40 mL of CSF to reduce CSF baclofen concentration.

Institute measures to support cardiovascular function.

In the event of convulsions, administer diazepam I.V. with caution.

DOSAGE AND ADMINISTRATION

Establishment of the optimum dose schedule requires that each patient undergoes an initial screening phase with intrathecal bolus, followed by a very careful individual dose titration prior to maintenance therapy. This is due to the great variability in the effective individual therapeutic dose.

General:

The first dose should be performed with resuscitative equipment on stand-by.

Patients must be monitored closely in a fully equipped and staffed environment during the screening phase and dose titration period immediately following implant. Resuscitative equipment should be available for immediate use in case of life threatening or intolerable adverse reactions. Implantation of pumps should only be performed in experienced centres in order to minimize the risks in the perioperative phase.

Screening phase:

Prior to initiation of chronic infusion of intrathecal baclofen, patients must demonstrate a response to intrathecal baclofen bolus in a screening trial. A test bolus dose of LIORESAL is usually administered via a lumbar puncture or an intrathecal catheter to elicit a response. For this purpose, low concentration ampoules of 0.05 mg/mL are available.

The usual initial test dose is 25 μg or 50 μg and is stepped up by 25 μg increments at least 24 hours apart, until an approximately 4- to 8-hour response is observed; the dose should be given by barbotage over at least one minute. If an adverse reaction occurs at a dose of 25 μg, a lower dose, such as 10 μg may be tested.

Patients should demonstrate a positive clinical response in order to be considered responders to treatment. A positive clinical response is characterized by a significant decrease in muscle tone and/or frequency and/or severity of spasms. There is great variability in sensitivity to intrathecal baclofen.

Patients who do not respond to a 100 μg test dose should not be given further increases of dose or be considered for continuous intrathecal infusion. However, in rare instances some patients, particularly those with spasticity of cerebral origin, have received higher test bolus doses.

Dose titration phase:
After confirmation that the patient is responsive to LIORESAL Intrathecal (baclofen injection) by means of test bolus doses, intrathecal infusion is established using a suitable delivery system. (See Drug delivery devices)

To determine the initial total daily dose of LIORESAL Intrathecal following implant, the screening dose which gave a positive effect should be doubled and administered over a 24-hour period, unless the efficacy of the bolus dose was maintained for more than 12 hours. In this case, the starting daily dose should be the screening dose delivered over a 24-hour period. No dose increases should be administered in the first 24 hours.

After the first 24 hours, the dosage should be adjusted slowly on a daily basis to achieve the desired effect, with dosage increments limited to 10 to 30% to avoid possible overdosing. With programmable pumps, the dose should be increased only once every 24 hours. For non-programmable pumps with a 76 cm catheter delivering 1 mL/day, intervals of 48 hours are

suggested for evaluation of response. If the daily dose has been significantly increased and no clinical effect is achieved, check for proper pump function and catheter patency.

The clinical goal is to maintain as normal a muscle tone as possible, and to minimize the frequency and severity of spasms without inducing intolerable side effects.

There is limited experience with doses greater than 1000 μg/day.

Maintenance therapy:
The lowest dose producing an adequate response should be used. Most patients require gradual increases in dose over time to maintain optimum response during chronic therapy due to decreased responsiveness to therapy or due to disease progression.

The daily dose may be gradually increased by 10 to 30% to maintain adequate symptom control by adjusting the dosing rate of the pump and/or the concentration of LIORESAL Intrathecal in the reservoir. The daily dose may also be reduced by 10 to 20% if patients experience side effects. A sudden requirement for substantial dose escalation suggests a catheter complication (i.e., catheter kink or dislodgement) or pump malfunction.

Maintenance dosage for long-term continuous infusion of intrathecal baclofen ranges from 10 μg/day to 1200 μg/day, most patients being adequately maintained on 300 μg/day to 800 μg/day. The specific concentration that should be used depends on the total daily dose required as well as the delivery rate of the pump. Please consult pump manufacturer's manual for specific recommendations.

During long-term treatment approximately 10% of patients become refractory to increasing doses. This ‘tolerance’ may be treated by gradually reducing LIORESAL Intrathecal dose over a 2 to 4 week period and switching to alternative methods of spasticity management (e.g. intrathecal preservative-free morphine sulfate). After a few days the sensitivity to baclofen may

be restored and treatment should be resumed at the initial continuous infusion dose and followed by a titration phase to avoid overdose accidents.

This must be performed in a hospital unit. Caution should be exercised when switching from LIORESAL Intrathecal to morphine and vice versa (see Precautions – Drug Interactions).

Regular clinical review remains a necessity throughout to assess dosage requirements, functioning of the delivery system, and monitoring for possible adverse drug reactions or evidence of infection.

Special populations:

Renal impairment

No studies have been performed in patients with renal impairment with LIORESAL Intrathecal therapy. Since baclofen is primarily eliminated unchanged through the kidneys, accumulation of unchanged drug in patients with renal impairment cannot be excluded (see CLINICAL PHARMACOLOGY).

LIORESAL Intrathecal 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 PRECAUTIONS, 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 receiving LIORESAL Intrathecal therapy. No dosage adjustment is recommended as the liver does not play any significant role in the metabolism of baclofen after intrathecal administration of LIORESAL. Therefore, hepatic impairment is not expected to impact the drug systemic exposure (see CLINICAL PHARMACOLOGY). 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.

Geriatrics

Several patients over the age of 65 years have been treated with LIORESAL Intrathecal during the clinical trials without increased risks compared to younger patients. Problems specific to this age group are not expected as doses are individually titrated (see WARNINGS, PRECAUTIONS and CLINICAL PHARMACOLOGY).

Delivery regimen:

LIORESAL Intrathecal is most often administered in a continuous infusion mode immediately following implant. After the patient has stabilized with regard to daily dose and functional status, and provided the pump allows it, a more complex mode of delivery may be started to optimize control of spasticity at different times of the day. For example, patients who have increased spasm at night may require a 20% increase in their hourly infusion rate. Changes in flow rate should be programmed to start two hours before the time of desired clinical effect.

Drug delivery devices:

Intrathecal administration of LIORESAL through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience. Specific instructions for programming and/or refilling the implantable pump are given by the pump manufacturers, and must be strictly adhered to. Consult pump manufacturer's literature for information on the appropriate use and care of these devices.

Evidence demonstrating the efficacy of LIORESAL Intrathecal was obtained using the Medtronic SynchroMed Programmable Infusion System. Other pumps proven to be suitable for intrathecal baclofen administration may be used.

The Medtronic SynchroMed II Programmable Infusion System is an implantable drug delivery system with refillable reservoirs which, after general or local anesthesia, is implanted in a subcutaneous pocket usually on the abdominal wall. This device is connected to an intrathecal catheter that passes subcutaneously to the subarachnoid space.

The Medtronic SynchroMed II Programmable Infusion System has either a 20 mL or 40 mL drug reservoir and may be programmed to different flow rates. The lithium hybrid cathode battery of the pump has a life span of 4 to 7 years and therefore requires replacement.

LIORESAL Intrathecal proved to be stable in the implanted SynchroMed II Programmable Infusion System for 180 days.

Details regarding the availability and use of this drug delivery device can be obtained from the manufacturer.

Medtronic of Canada Ltd.
99 Hereford Street
Brampton, Ontario
L6Y 0R3
Phone: 1 (800) 268 5346
website: www.medtronic.ca

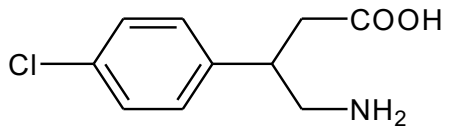
General guidelines regarding the use of all implantable systems are located under PRECAUTIONS.

Before using other systems, it must be confirmed that the technical specifications, including

chemical stability of baclofen in the reservoir fulfil the requirements for safe and effective use of LIORESAL Intrathecal. Please consult pump manufacturer's manual for this information.

PHARMACEUTICAL INFORMATION

Drug Substance:



Baclofen

Chemical Name: 4-amino-3-(p-chlorophenyl) butyric acid

Molecular Formula: $C_{10}H_{12}ClNO_2$

Molecular Weight: 213.67

Description: White to off-white, odorless or practically odorless crystalline powder.

Solubility: Slightly soluble in water, very slightly soluble in methanol and insoluble in chloroform.

pK_a: $pK_{a,\,1}$ = 3.87 (carboxyl group) and $pK_{a,\,2}$ = 9.62 (amino group) in water at 20^{O}C.

Composition:

The contents of each sterile ampoule are described in the following table.

Dosage mg/mL	Total Volume mL	Medicinal ingredient	Non-medicinal ingredients	
		Baclofen/mg	Sodium chloride/mg	Water for injection
0.05	1	0.05	9	up to 1 mL
0.5	20	10	180	up to 20 mL
2.0	5	10	45	up to 5 mL

Stability and Storage Recommendations:

Protect from heat (store at 15-30°C). Do not freeze. Do not heat sterilize.

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

Parenteral Products:

Instructions for use/handling:
LIORESAL Intrathecal is intended for intrathecal injection and continuous intrathecal infusion as indicated by the delivery specifications of the infusion system.

Each ampoule is intended for single use only. Discard any unused portion.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration whenever solution and container permit.

The concentration to be used depends upon the total daily dose required as well as the delivery rate of the pump. Please consult manufacturer's manual for specific recommendations.

For patients who require concentrations other than 0.05 mg/mL, 0.5 mg/mL or 2.0 mg/mL, LIORESAL Intrathecal must be diluted, under aseptic conditions, with sterile preservative-free sodium chloride injection and used immediately.

As a rule LIORESAL ampoules for intrathecal administration should not be mixed with other infusion or injection solutions. Dextrose proved to be incompatible due to a chemical reaction with baclofen.

AVAILABILITY OF DOSAGE FORMS

LIORESAL Intrathecal (baclofen injection) 0.05 mg/mL:
Each 1 mL ampoule of clear, colorless solution contains 0.05 mg baclofen for intrathecal administration.

LIORESAL Intrathecal (baclofen injection) 0.5 mg/mL:

Each 20 mL ampoule of clear, colorless solution contains 10 mg baclofen for intrathecal administration.

LIORESAL Intrathecal (baclofen injection) 2 mg/mL:
Each 5 mL ampoule of clear, colourless solution contains 10 mg baclofen for intrathecal administration.

LIORESAL Intrathecal 0.05 mg/mL and 2 mg/mL are provided in cartons of 5 ampoules.
LIORESAL Intrathecal 0.5 mg/mL is provided in cartons of 1 ampoule.

PHARMACOLOGY

Primary Pharmacological Activity:
Baclofen depresses monosynaptic and polysynaptic reflex transmission in the spinal cord. The antispastic activity is derived primarily from its action at the spinal level to reduce spasms in voluntary muscles (see also LIORESAL Product Monograph).

Secondary Pharmacological Activity:
Intrathecal baclofen exerts an antinociceptive effect in rats and cats. These effects are independent of any debilitation of voluntary motor function. In addition, intrathecal baclofen affects lower urinary tract dynamics of the anesthetized dog. Vesical and urethral pressure was significantly decreased. Within 30 minutes of injection, relaxation of the bladder and a reduction in urethral resistance occurred.

TOXICOLOGY

Acute Toxicity
LD_{50} values following intrathecal dosing are not available.

Long-Term Toxicity

The oral toxicity of LIORESAL has been thoroughly investigated. LIORESAL Intrathecal requires the use of much smaller doses to achieve a therapeutic effect, with consequential lower systemic exposure.

Repeated dose toxicity

Repeated intrathecal administration of baclofen to rats and dogs was not associated with irritation or inflammation of the spinal cord and surrounding tissues. Inflammation of the spinal cord was observed in one rabbit in a study that administered intrathecal baclofen to 3 rabbits weekly over a period of 3 to 6 months.

Local tolerance

Subacute and subchronic studies with continuous intrathecal baclofen infusion in two species (rat, dog) revealed no signs of local irritation or inflammation on histological examination. Preclinical studies in animal models have demonstrated that the formation of inflammatory mass is directly related to high dose and/or high concentration of intrathecal opioids and no inflammatory mass is formed with intrathecal baclofen as a sole agent.

Teratology and Reproduction studies

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 postpartum. In a third study, baclofen doses of 30 mg/kg/day produces 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 2/293 fetuses from dams receiving 20 mg/kg/day had abdominal hernias (See also WARNINGS). 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 hindlimbs in the fetuses from the high dose group. In another study, a slight increase in resorption rates was observed in rabbits receiving 10 and 15 mg/kg/day of oral baclofen.

Baclofen did not cause teratogenic effects in mice, rats, and rabbits at doses up to125-times the maximum intrathecal mg/kg dose. LIORESAL given orally increased the incidence of omphaloceles (ventral hernias) in fetuses of rats given approximately 500-times the maximum intrathecal dose expressed as a mg/kg dose. This abnormality was not seen in mice or rabbits. LIORESAL dosed orally caused delayed fetal growth (ossification of bones) at doses that also caused maternal toxicity in rats and rabbits, and when given intraperitoneally, baclofen at high doses caused widening of the vertebral arch in rat fetuses.

Carcinogenicity studies

A 2-year rat study (oral administration) showed that baclofen is not carcinogenic. In the same study a dose-related increase in incidence of ovarian cysts and a less marked increase in enlarged and/or hemorrhagic adrenal glands was observed.

Mutagenicity Studies

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

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PART III: CONSUMER INFORMATION

PrLIORESAL® Intrathecal
(baclofen injection)
0.05 mg/mL, 0.5 mg/mL and 2 mg/mL
For intrathecal injection and infusion only

This leaflet is part III of a three-part "Product Monograph" published when LIORESAL® IT 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® IT. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

LIORESAL Intrathecal belongs to a group of medicines called muscle relaxants. It is used to reduce and relieve the excessive stiffness and/or spasms occurring in various illnesses such as, for example, multiple sclerosis, diseases or injuries of the spinal cord, and certain brain disorders.

What it does:

The solution is injected or infused into the fluid space around the spinal cord by use of a special pump which is implanted under the skin of your abdomen. From the pump a constant amount of the solution is delivered into the fluid space around the spinal cord through a tiny tube.

Due to the beneficial effect on muscle contractions and the consequent relief from pain, LIORESAL Intrathecal improves your mobility and your ability to manage your daily activities without aid. LIORESAL also helps you to benefit more from physiotherapy.

When it should not be used:

You should not be treated with LIORESAL IT if you:
- are allergic (hypersensitivity) to LIORESAL Intrathecal or any of the other ingredients of LIORESAL Intrathecal listed below.

What the medicinal ingredient is:
baclofen.

What the nonmedicinal ingredients are:

LIORESAL IT contains: sodium chloride and water for injection

What dosage forms it comes in:

LIORESAL Intrathecal (baclofen injection) 0.05 mg/mL: Each 1 mL ampoule contains 0.05 mg baclofen for intrathecal administration.

LIORESAL Intrathecal (baclofen injection) 0.5 mg/mL: Each 20 mL ampoule contains 10 mg baclofen for intrathecal administration.

LIORESAL Intrathecal (baclofen injection) 2 mg/mL: Each 5 mL ampoule contains 10 mg baclofen for intrathecal administration.

WARNINGS AND PRECAUTIONS

LIORESAL Intrathecal is suitable for many, but not all, patients with muscle spasms.

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

- have any kind of infection
- have Parkinson's disease or certain mental illnesses accompanied by confusion
- have epilepsy (seizures)
- have diabetes
- ever had heart problems
- ever had kidney problems
- have breathing problems
- have acute pain in your stomach or intestine
- have abnormal blood circulation in your brain
- have ever experienced sudden episodes of high blood pressure, anxiety, excessive sweating, "goose flesh", a pounding headache, and an unusually slow heartbeat due to an overreaction of your nervous system to stimuli such as distension of the bladder and intestine, skin irritation and pain

If any of these apply to you, your doctor may not want to give you this medicine or may want to take special precautions. If you have not told your doctor about any of these things, tell him/her before you start LIORESAL Intrathecal treatment.

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

Get urgent medical help if you observe that your implanted device is not working and you also notice withdrawal symptoms (see Missed dose).

Tell your doctor immediately if you get any of these symptoms during treatment with LIORESAL Intrathecal:

- **If you have pain** in your back, shoulders, neck and buttock during the treatment (a type of spinal deformity called scoliosis)
- **If you 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 behaviour and ask them to read this leaflet.

Driving and using machines: LIORESAL Intrathecal may make you feel sleepy or dizzy. Be careful when driving a car or using a machine or doing things that need careful attention until you are feeling normal again.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including herbal and non- prescription medicines (over the counter). Some other medicines may interact with LIORESALIT. Your doctor may change the dosage or sometimes stop one of the medicines. This is particularly important for the following medicines:

- other medicines for your spastic condition
- medicines for Parkinson' disease
- medicines for epilepsy
- medicines used to treat mood disorders such as antidepressants and lithium
- medicines for high blood pressure
- other drugs which affect the kidney, e.g. ibuprofen
- opiates for pain relief
- medicines used to help you sleep or calm you down
- medicines which slow down the central nervous system, e.g. anti-histamines and sedatives (some of these can be bought over the counter)

Always tell your doctor or nurse about all the medicines you are taking. This means medicines you have bought yourself as well as medicines on prescription from your doctor.

Be careful if you drink alcoholic beverages during treatment with LIORESAL Intrathecal as you may feel more sleepy or dizzy than usual.

PROPER USE OF THIS MEDICATION

Usual dose:

LIORESAL Intrathecal can only be given by experienced doctors using special medical equipment. You will need to stay in hospital, at least at the beginning of treatment.

Your doctor will inject a small amount of LIORESAL Intrathecal into your spinal cord to see if it improves your muscle spasms. If it does, then a special pump will be implanted under your skin. The pump will give you a small amount of medicine all the time.

It may take several days to find out the amount of medicine that suits you best, your doctor will keep a close watch on you during this time.

After that, your doctor will still want to see you regularly to check your progress and make sure your pump is working well.

IT IS OF UTMOST IMPORTANCE THAT APPOINTMENTS TO REFILL THE PUMP ARE KEPT, OTHERWISE SPASMS MAY RECUR BECAUSE YOU ARE NOT GETTING A HIGH ENOUGH DOSE OF LIORESAL INTRATHECAL. MUSCLE SPASTICITY MAY NOT IMPROVE OR MAY WORSEN AS A RESULT.

If muscle spasticity is not improving or if you start having spasms again, either gradually or suddenly, contact your doctor immediately.

Please consult the pump manufacturer's literature for information regarding proper home care of the pump and the insertion site.

Monitoring during treatment with LIORESAL Intrathecal

You will be monitored closely in a fully equipped and staffed environment during the screening phase and dose-titration period immediately following pump implant. You will regularly be assessed for your dosage requirements, for possible side effects or evidence of infection. The functioning of the delivery system will also be checked.

Pregnancy and breast-feeding

You should tell your doctor if you are pregnant, or planning to become pregnant as LIORESAL Intrathecal should not be used during pregnancy, or if you are breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine.

Your doctor will discuss with you the potential risk of taking LIORESAL Intrathecal during pregnancy. Use of LIORESAL Intrathecal 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. The doctor will decide if you may receive LIORESAL Intrathecal in these special situations. Only very small quantities of LIORESAL pass into the breast milk. Ask your doctor if you want to breast-feed.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Signs of overdose may appear suddenly or insidiously e.g. by a malfunctioning of the pump. It is very important that you and those caring for you recognize signs of overdosage. If you experience any one or a combination of the following symptoms, tell your doctor without delay as the amount of drug you receive may be too high:

- unusual muscular weakness (too little muscle tone)
- sleepiness
- lightheadedness or dizziness
- excessive salivation
- nausea or vomiting
- difficulties in breathing, seizures or loss of consciousness
- abnormal low body temperature

Missed Dose:

Abruptly stopping LIORESAL Intrathecal can result in serious medical problems and in rare cases has been fatal.

Signs that your pump is not functioning properly or that it is not delivering the right amount of medication include an increase or return in spasticity, itching, low blood pressure, lightheadedness, tingling sensation, high fever, altered mental status, muscle rigidity or new muscle weakness or paralysis, persistent erection of the penis (priapism) and infection (sepsis). It is important to tell your doctor immediately if you experience any of the above symptoms. These signs may be followed by more serious side effects (including death) unless you are treated immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with all medicines, patients treated with LIORESAL Intrathecal, may experience some side effects, although not everybody gets them. These occur more often at the start of treatment during your hospital stay but they may also occur later and should be checked with your doctor.

Very common: Drowsiness, muscle weakness

Common: Feeling of anxiety, sedation and weariness (exhaustion), weakness in the legs, stiffness in the muscles, dizziness/light-headedness, headache, sleepiness, feeling sick and/or vomiting, tingling in the hands and feet, insomnia, slurred speech, pneumonia, weakness, chills, fatigue, pain, dry mouth, skin rash and/or itching, swelling of the ankles, feet, or lower legs, puffy face, unusual nervousness or restlessness, confusion/disorientation, constipation, diarrhea, decreased appetite, excessive salivation, fever/shivering, urinary problems, sexual difficulties.

Uncommon: Mood or mental changes, paranoia, feeling extreme happiness (euphoria), loss of muscle coordination (ataxia), abnormally low body temperature, memory loss, continuous uncontrollable eye movements, decreased sense of taste, difficulty in swallowing, abdominal pain, hair loss, excessive sweating.

Unknown frequency: restlessness (dysphoria), abnormally slow breathing rate (bradypnea), increase

in sideways curvature of the spine (scoliosis), inability to achieve or maintain an erection (erectile dysfunction).

Tell your doctor if you notice any other effect. Some side effects could be associated with the delivery system.

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 immediately seek assistance
		Only if severe	In all cases	
Common	**Low Blood Pressure:** dizziness, fainting, lightheadedness		√	
	Trouble breathing: Shortness of breath or unusually slow or troubled breathing		√	
Uncommon	Unusually slow heartbeat		√	
	Depression: Feeling sad, loss of interest in usual activities, hopelessness, insomnia or sleeping too much	√		
	Suicidal Behavior: thoughts or actions about hurting or killing yourself		√	
	Hallucinations: seeing or hearing things that are not real		√	
	Trouble with vision: blurred vision, double vision	√		
Unknown	Implanted drug delivery device or infusion system malfunction can lead to withdrawal symptoms including death		√	

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

HOW TO STORE IT

Store LIORESAL IT ampoules between 15-30°C (protect from heat). Do not freeze. Do not heat sterilize.

Keep all medicines out of the reach and sight of children.

This medicine is prescribed for your specific medical problem and for your own use only. Do not give to other people.

Do not use outdated medicines. Discard them safely out of the reach of children or take them to your pharmacist who will dispose of them for you.

REPORTING SUSPECTED SIDE EFFECTS

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

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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