NEW ZEALAND DATA SHEET

LIORESAL® INTRATHECAL

Baclofen

0.05mg/1mL Solution for Intrathecal injection

1. PRODUCT NAME

Lioresal® Intrathecal 0.05 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lioresal Intrathecal is a solution for intrathecal injection. It contains no preservatives.

One ampoule of 1 mL contains 0.05 mg baclofen (0.05 mg/mL).

3. PHARMACEUTICAL FORM

Lioresal ampoules containing 0.05 mg/mL are available for administering low-dose bolus injections during the screening phase.

Lioresal Intrathecal contains no preservatives.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lioresal Intrathecal is indicated in patients with severe chronic spasticity of spinal origin (associated with injury, multiple sclerosis, or other spinal cord diseases) or of cerebral origin who are unresponsive to orally administered antispastics (including oral baclofen) and/or who experience unacceptable side effects at effective oral doses.

4.2 Dose and method of administration

Dosage

Lioresal Intrathecal is intended for administration in single bolus test doses (via spinal catheter or lumbar puncture).

For patients with spasticity due to head injury, it is recommended not to proceed to long-term Lioresal Intrathecal therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

Establishment of the optimum dose schedule requires that each patient undergoes an initial screening phase with test doses by 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.

Patients must be monitored closely in a fully equipped and staffed environment during the screening phase and dose-titration period. Resuscitative equipment should be available for immediate use in case of life-threatening or intolerable adverse reactions.

Screening phase

Prior to initiation of chronic infusion of intrathecal baclofen, patients must demonstrate a response to an intrathecal bolus of baclofen in a screening trial. A bolus test dose of baclofen

is usually administered via a lumbar puncture or an intrathecal catheter to elicit a response. In adults, the usual initial test dose is 25 micrograms or 50 micrograms and is stepped up by 25 microgram increments at least 24 hours apart, until a response lasting approximately 4 to 8 hours is observed; the dose should be given by barbotage over at least one minute. In children, the recommended initial test dose is 25 micrograms. For the test dose, low concentration ampoules of 0.05 mg/mL are available.

The first dose should be performed with resuscitative equipment on stand-by. Patients should demonstrate a significant decrease in muscle tone and/or frequency and/or severity of spasms in order to be considered responders to treatment.

There is great variability in sensitivity to intrathecal baclofen. Signs of severe overdose (coma), have been observed in an adult patient after a single test dose of 25 micrograms.

Patients who do not respond to a 100 microgram test dose should not be given further increases of dose or be considered for continuous intrathecal infusion.

Dose titration phase

After confirmation that the patient is responsive to intrathecal baclofen by means of bolus test doses, intrathecal infusion is established using a suitable delivery system. Please refer to the full New Zealand data sheet for baclofen intrathecal infusion.

Special populations

Renal impairment

No studies have been performed in patients with renal impairment with Lioresal Intrathecal therapy. Because baclofen is primarily excreted unchanged by the kidneys (see Section 5 Pharmacological properties) it should be given with special care and caution in patients with impaired renal function (see Section 4.4 Special warnings and precautions for use).

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 Section 5 Pharmacological properties).

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 Section 4.4 Special warnings and precautions for use and Section 5 Pharmacological properties).

4.3 Contraindications

- Known hypersensitivity to baclofen or to any of the excipients.
- The drug should not be administered by the intravenous, intramuscular, epidural or subcutaneous routes.
- Epilepsy refractory to therapy.

4.4 Special warnings and precautions for use

Withdrawal effects (including associated with catheter or device malfunction)

Except in overdose-related emergencies, treatment with Lioresal Intrathecal should always be gradually discontinued by successively reducing the dosage. Lioresal Intrathecal should not be discontinued suddenly (applicable to maintenance therapy).

Abrupt withdrawal of intrathecal baclofen, regardless of the cause, has resulted in sequelae that included high fever, tachycardia, altered mental status, exaggerated rebound spasticity and muscle rigidity that in rare cases progressed to seizures/status epilepticus, coagulopathy, rhabdomyolysis, multiple organ-system failure and death. In the first 9 years of post-marketing experience, 27 cases of withdrawal temporally related to the cessation of baclofen therapy were reported; six patients died. In most cases, symptoms of withdrawal appeared within hours to a few days following interruption of baclofen therapy.

All patients receiving intrathecal baclofen therapy are potentially at risk for withdrawal. Early symptoms of baclofen withdrawal may include return of baseline spasticity, pruritus, hypotension and paraesthesias. Some clinical characteristics of the advanced intrathecal baclofen 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 intrathecal baclofen withdrawal. The suggested treatment for intrathecal baclofen withdrawal is the restoration of intrathecal baclofen 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 or enteral baclofen or oral, enteral or intravenous benzodiazepines may prevent potentially fatal sequelae. Oral or enteral baclofen alone should not be relied upon to halt the progression of intrathecal baclofen withdrawal. Seizures have been reported during overdose and with withdrawal from Lioresal Intrathecal as well as in patients maintained on therapeutic doses of baclofen.

Please refer to the full New Zealand data sheet for baclofen intrathecal infusion.

Screening phase

The infusion pump system should not be implanted until the patient's response to bolus intrathecal baclofen injection and/or dose titration is adequately evaluated and found to be clinically safe and effective. Because of the risks associated with the initial administration and titration of intrathecal baclofen (CNS depression, cardiovascular collapse and/or respiratory failure), these steps must be conducted in a medically supervised and adequately equipped environment, following the instructions outlined in Section 4.2 Dose and method of administration.

The preliminary screening phase should be performed in a hospital and implantation of the pump system should be undertaken only in specialist units. Resuscitative equipment should be available for immediate use in case of life-threatening symptoms of severe overdose.

Careful monitoring of respiratory and cardiovascular functions is essential during administration of the initial test doses (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.

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

Before use of the drug, myelography of the subarachnoid space should be performed in patients with postraumatic spasticity. If signs of arachnoiditis are detected, treatment should not be given.

Repeated dose toxicity

Repeated intrathecal administration of baclofen was not associated with the development of inflammatory masses in studies in rats and dogs. No changes to the spinal cord and adjacent tissue and no signs of irritation or inflammation of the spinal cord and surrounding tissues were noted in either species.

Scoliosis

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

Additional considerations pertaining to dosage adjustment

In order to prevent excessive weakness and falling, intrathecal baclofen should be used with caution when spasticity is needed to sustain upright posture and balance in locomotion or whenever spasticity is used to obtain optimal function and care. 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.

Withdrawal of oral antispastic medication

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

Precautions in special patient populations

In patients with **abnormal CSF flow** the distribution of baclofen and its antispastic activity may be inadequate.

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

Psychiatric and nervous system disorders

Suicide and suicide-related events have been reported in patients treated with baclofen. In most cases, the patients had additional risk factors associated with an increased risk of suicide including alcohol use disorder, depression and/or a history of previous suicide attempts. Close

supervision of patients with additional risk factors for suicide should accompany 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.

Epilepsy

Special attention should be given to patients known to suffer from **epilepsy** or with a history of seizures, since seizures have been reported occasionally during overdose with, or withdrawal from, intrathecal baclofen, as well as in patients maintained on therapeutic doses of intrathecal baclofen.

Autonomic dysreflexia

Intrathecal baclofen should be used with caution in patients with a history of **autonomic dysreflexia**. The presence of nociceptive stimuli on abrupt withdrawal of Lioresal Intrathecal may cause an autonomic dysreflexic episode (see Section 4.4 Special warnings and precautions for use - withdrawal effects (including associated with catheter or device malfunction).

Cerebrovascular or respiratory insufficiency

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

Non-CNS related diseases

An effect of intrathecal baclofen on **underlying, non-CNS related diseases** is unlikely because the systemic availability of the drug after intrathecal administration is substantially lower than after oral administration. Caution should be exercised in patients with history of peptic ulcers and based on observations after oral baclofen therapy, in those with pre-existing sphincter hypertonia.

Renal impairment

After **oral** Lioresal dosing severe neurological outcomes have been reported in patients with renal impairment. Thus caution should be exercised while administering Lioresal Intrathecal in patients with renal impairment.

Paediatric patients (below 18 years)

For patients with spasticity due to head injury, it is recommended not to proceed to long-term baclofen intrathecal therapy until the symptoms of spasticity are stable (i.e. at least one year after the injury).

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Use of baclofen intrathecal in the paediatric population should be only prescribed by medical specialists with the necessary knowledge and experience. There are very limited clinical data on the use of intrathecal baclofen in children under age six. The safe use of intrathecal baclofen in children under the age of four has not yet been established.

Use in the elderly (65 years of age or above)

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.

4.5 Interaction with other medicines and other forms of interaction

There is little experience with the use of intrathecal baclofen 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 Section 5.2 Pharmacokinetic properties).

Anticipated interactions resulting in concomitant use not being recommended

Levodopa/DDC inhibitor

Concomitant use of **oral** Lioresal and levodopa/DDC inhibitor resulted in increased risk of adverse events like visual hallucinations, confusional state, headache and nausea. Worsening of the symptoms of Parkinsonism has also been reported. Thus, caution should be exercised when intrathecal Lioresal is administered to patients receiving levodopa/DDC inhibitor therapy.

Observed interactions to be considered

Anaesthetics

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.

Antihypertensives and other drugs known to lower blood pressure

Since concomitant treatment with drugs that lower blood pressure is likely to further increase a possible fall in blood pressure, dosage of the concomitant medications should be adjusted accordingly.

Anticipated interactions to be considered

Morphine

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

The co-administration of other intrathecal agents with intrathecal baclofen has not been tested and its safety is unknown.

Alcohol and other compounds affecting the 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 baclofen.

Tricyclic antidepressants

When using **oral** baclofen, concurrent treatment with tricyclic antidepressants may potentiate the effect of baclofen, resulting in pronounced muscular hypotonia. Caution is advised when using intrathecal baclofen in this combination.

4.6 Fertility, pregnancy and lactation

Fertility

Animal studies have shown that intrathecal baclofen is unlikely to have an adverse effect on fertility under clinically-relevant conditions.

Women of child-bearing potential

There are no special recommendations for women of child-bearing potential.

Use in pregnancy (Category B3)

There is limited data on the use of Lioresal Intrathecal in pregnant women.

After intrathecal administration of Lioresal small amounts of baclofen can be detected in maternal plasma (see section 5 Pharmacological properties). Animal data showed that baclofen can cross the placental barrier. Therefore, Lioresal Intrathecal should not be used during pregnancy unless the expected benefit outweighs the potential risk to the fetus.

Lioresal is not teratogenic in mice, rats and rabbits at doses at least 125-times the maximum intrathecal mg/kg dose. Lioresal given **orally** has been shown to increase 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** has been shown to cause delayed fetal growth (ossification of bones) at doses that also caused maternal toxicity in rats and rabbits. Baclofen caused widening of the vertebral arch in rat fetuses at a high intraperitoneal dose.

Breastfeeding

After oral administration of baclofen at therapeutic doses, baclofen passes into the breast milk, but in quantities so small that no undesirable effects on the infant are to be expected.

After intrathecal administration of Lioresal small amounts of baclofen can be detected in maternal plasma. (see section 5 Pharmacological properties). Therefore, no baclofen is expected to be found in the milk of the mother receiving Lioresal Intrathecal therapy and no special recommendations are given.

4.7 Effects on ability to drive and use machines

Central nervous system (CNS) depressant effects such as somnolence and sedation have been reported in some patients receiving intrathecal baclofen. Other listed events include ataxia, hallucinations, diplopia and withdrawal symptoms. Patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness.

4.8 Undesirable effects

Clinical trials in patients with spasticity of spinal origin

Adverse experiences reported during US studies (both controlled and uncontrolled) are shown in the following table. None of these adverse experiences led to discontinuation of treatment.

INCIDENCE OF MOST FREQUENT ADVERSE EVENTS IN PATIENTS WITH SPASTICITY OF SPINAL ORIGIN IN PROSPECTIVELY MONITORED CLINICAL TRIALS CONDUCTED IN THE US

Adverse Event	Number of Patients Reporting Events		
	N = 244 Screening[a]	N = 214 Titration[b]	N = 214 Maintenance[c]
Drowsiness	13	11	18
Weakness, Lower Extremities	1	11	15
Dizziness/Light-headedness	6	5	12
Seizures	1	4	11
Headache	0	3	9
Nausea/Vomiting	3	5	3
Numbness/Itching/Tingling	2	1	8
Hypotension	3	0	5
Blurred Vision	0	2	5
Constipation	0	2	5
Hypotonia	2	3	2
Speech Slurred	0	1	6
Coma (Overdose)	0	4	3
Lethargy	1	0	4
Weakness, Upper Extremities	1	0	4
Hypertension	1	2	2
Dyspnoea	1	2	1

[a] Following administration of test bolus
[b] Two month period following implant
[c] Beyond two months following implant
(N = total number of patients entering each period).

Clinical trials in patients with spasticity of cerebral origin

Adverse experiences reported during US studies (both controlled and uncontrolled) are shown in the following table. Nine patients discontinued long-term treatment due to adverse events.

INCIDENCE OF MOST FREQUENT (≥ 1%) ADVERSE EVENTS IN PATIENTS WITH SPASTICITY OF CEREBRAL ORIGIN IN PROSPECTIVELY MONITORED CLINICAL TRIALS CONDUCTED IN THE US

Adverse Event	Number and Percent (%) of Patients Reporting Events		
	N = 211 Screening[a]	N = 153 Titration[b]	N = 150 Maintenance[c]
Hypotonia	5 (2.4)	22 (14.4)	52 (34.7)
Somnolence	16 (7.6)	16 (10.5)	28 (18.7)
Headache	14 (6.6)	12 (7.8)	16 (10.7)

Nausea and vomiting	14 (6.6)	16 (10.5)	6 (4.0)
Vomiting	13 (6.2)	13 (8.5)	6 (4.0)
Urinary retention	2 (0.9)	10 (6.5)	12 (8.0)
Seizures	2 (0.9)	5 (3.3)	15 (10.0)
Dizziness	5 (2.4)	4 (2.6)	12 (8.0)
Nausea	3 (1.4)	5 (3.3)	11 (7.3)
Hypoventilation	3 (1.4)	2 (1.3)	6 (4.0)
Hypertonia	0 (0.0)	1 (0.7)	9 (6.0)
Paraesthesia	4 (1.9)	1 (0.7)	5 (3.3)
Hypotension	4 (1.9)	1 (0.7)	3 (2.0)
Increased salivation	0 (0.0)	4 (2.6)	4 (2.7)
Back pain	2 (0.9)	1 (0.7)	3 (2.0)
Constipation	1 (0.5)	2 (1.3)	3 (2.0)
Pain	0 (0.0)	0 (0.0)	6 (4.0)
Pruritus	0 (0.0)	0 (0.0)	6 (4.0)
Diarrhoea	1 (0.5)	1 (0.7)	3 (2.0)
Peripheral oedema	0 (0.0)	0 (0.0)	5 (3.3)
Thinking abnormal	1 (0.5)	2 (1.3)	1 (0.7)
Agitation	1 (0.5)	0 (0.0)	2 (1.3)
Asthenia	0 (0.0)	0 (0.0)	3 (2.0)
Chills	1 (0.5)	0 (0.0)	2 (1.3)
Coma	1 (0.5)	0 (0.0)	2 (1.3)
Dry mouth	1 (0.5)	0 (0.0)	2 (1.3)
Pneumonia	0 (0.0)	0 (0.0)	3 (2.0)
Tremor	1 (0.5)	0 (0.0)	2 (1.3)
Urinary incontinence	0 (0.0)	0 (0.0)	3 (2.0)
Urination impaired	0 (0.0)	0 (0.0)	3 (2.0)

a Following administration of test bolus

b Two month period following implant

c Beyond two months following implant

(N = total number of patients entering each period. 211 patients received drug. 1 of 212 received placebo only)

Some of the adverse events listed below have been reported in patients with spasticity of spinal origin but could also occur in patients with spasticity of cerebral origin. Adverse events that are more frequent in either population are indicated below.

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials are listed 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.

Metabolism and nutrition disorders	
Uncommon:	Dehydration.
Psychiatric disorders	
Common:	Depression, anxiety, agitation, insomnia, confusional state.

Uncommon:	Suicidal ideation, suicide attempt, hallucinations, paranoia, euphoric mood.
Nervous system disorders	
Very common:	Somnolence.
Common:	Convulsions, , sedation, dizziness, headache, paraesthesiae, dysarthria, lethargy, , disorientation.
Uncommon:	Ataxia, memory impairment, nystagmus. Convulsion and headache occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.
Eye disorders	
Common	Accommodation disorder, vision blurred, diplopia.
Cardiac disorders	
Uncommon	Bradycardia.
Vascular disorders	
Common	Hypotension.
Uncommon	Hypertension, deep vein thrombosis, flushing, pallor.
Respiratory, thoracic and mediastinal disorders	
Common	Respiratory depression, pneumonia, dyspnoea.
Gastrointestinal disorders	
Common	Nausea, vomiting, constipation, dry mouth, diarrhoea, decreased appetite, increased salivation
Uncommon	Ileus, dysphagia, hypogeusia. Nausea and vomiting occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.
Skin and subcutaneous tissue disorders	
Common	Urticaria, pruritus, facial and/or peripheral oedema.
Uncommon	Alopecia, hyperhydrosis.
Renal and urinary disorders	
Common	Urinary incontinence, urinary retention. Urinary retention occurs more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.
Musculoskeletal and connective tissue disorders	
Very common	Hypotonia.
Common	Hypertonia.
Reproduction system and breast disorders	
Common	Sexual dysfunction.
General disorders and administration side conditions	
Common	Asthenia, pyrexia, pain, chills.
Uncommon	Hypothermia.
Rare	Life-threatening withdrawal symptoms due to drug delivery failure (see section 4.4 Special warnings and precautions for use).

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: bradypnoea.

Musculoskeletal and connective tissue disorders: scoliosis (see Section 4.4 Special warnings and precautions for use).

Reproductive system breast disorders: erectile dysfunction.

Immune system disorders: hypersensitivity

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

Deaths due to overdose of intrathecal baclofen have been reported. Special attention must be given to recognising the signs and symptoms of overdosage at all times, especially during the initial "screening" and "dose-titration" phase of treatment but also during reintroduction of intrathecal baclofen after a period of interruption of therapy. Signs of overdose may appear suddenly or insidiously.

Excessively rapid dose increases and concomitant treatment with oral baclofen are possible causes of overdosage Symptoms of severe intrathecal baclofen overdose (coma) were reported in a sensitive adult patient after receiving a 25 microgram intrathecal bolus dose.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

Symptoms

Excessive muscular hypotonia, drowsiness, light-headedness, dizziness, somnolence, seizures, loss of consciousness, hypothermia, excessive salivation, nausea, vomiting, tachycardia and tinnitus. Respiratory depression, bradycardia, apnoea and coma result from serious overdosage.

Treatment

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

1. Residual baclofen solution should be removed from the pump as soon as possible.
2. Patients with respiratory depression should be intubated and ventilated, if necessary, until the drug is eliminated.
3. If lumbar puncture is not contraindicated, consideration should be given, in the early stage of the intoxication, to withdrawing 30 - 40 mL of CSF to reduce CSF baclofen concentration.

4. Cardiovascular function should be supported.

5. In the event of convulsions, diazepam may be administered cautiously i.v.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: MO3BX Other centrally acting agents, ATC code: MO3BXO1.

Baclofen is an antispastic agent with a spinal site of action. Baclofen also has central sites of action given the adverse event profile. Baclofen is a racemic mixture of the R, (-) and S, (+) isomers. Experimental data indicate that the pharmacological action resides in the R, (-) isomer.

The precise mechanisms of action of baclofen as a muscle relaxant and antispastic agent are not fully understood. Baclofen depresses both monosynaptic and polysynaptic reflex transmission in the spinal cord, 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 stimulating $GABA_{\beta}$ receptors. Neuromuscular transmission is not affected. Baclofen exerts an antinociceptive effect. In neurological diseases associated with spasm of the skeletal muscles (for e.g. tetanus), the clinical effects of baclofen take the form of a beneficial action on reflex muscle contractions and of marked relief from painful spasm, automatism, hyperreflexia, trismus and clonus.

Baclofen improves patient mobility and facilitates physiotherapy. The above effects result in improved ambulation, prevention and healing of decubitus ulcers and better sleep patterns due to elimination of painful muscle spasms. In addition, patients experience improvement in bladder and sphincter function and catheterisation is made easier, all representing significant improvements in the patient's quality of life.

Baclofen has been shown to have general CNS depressant properties, causing sedation, somnolence, and respiratory and cardiovascular depression. It has also been shown to have a dose-dependent inhibitory effect on erectile function in men through $GABA_B$ receptor stimulation.

Baclofen introduced directly into the intrathecal space permits effective treatment of spasticity with doses at least 100 times smaller than those for oral administration.

Intrathecal baclofen may be considered an alternative to destructive neurosurgical procedures.

There is also some limited evidence of efficacy in reducing spasms in patients with tetanus.

Clinical efficacy and safety

Spasticity of spinal origin

Evidence supporting the efficacy of Lioresal Intrathecal was obtained in randomised, controlled investigations that compared the effects of either a single intrathecal dose or a three day intrathecal infusion of Lioresal Intrathecal to placebo in patients with severe spasticity and spasms due to either spinal cord trauma or multiple sclerosis. Lioresal Intrathecal was superior to placebo on both principal outcome measures employed: change from baseline in the Ashworth rating of spasticity and the frequency of spasms.

Spasticity of cerebral origin

The efficacy of Lioresal Intrathecal was investigated in three controlled clinical trials. Two enrolled patients with cerebral palsy and one enrolled patients with spasticity due to previous brain injury. The first study, a randomised controlled crossover trial of 51 patients with cerebral palsy, provided strong, statistically significant results and was considered to be the pivotal study. Lioresal Intrathecal was superior to placebo in reducing spasticity as measured by the Ashworth scale. A second crossover study was conducted in 11 patients with spasticity arising from brain injury. Despite the small sample size, the study yielded a nearly significant test statistic ($p = 0.066$) and provided directionally favourable results. The last study did not provide data that could be reliably analysed. However, data on the effects of a 50 microgram dose of Lioresal Intrathecal in both the second and third studies were consistent with the results of the pivotal study.

In the USA, there were three deaths occurring among 211 patients treated with Lioresal Intrathecal in pre-marketing studies as of March 1996. These deaths were not attributed to the therapy.

5.2 Pharmacokinetic properties

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

Absorption

Direct infusion into the spinal subarachnoid space by-passes absorption processes and allows exposure to the receptor sites in the dorsal horn of the spinal cord.

Onset of action

Intrathecal bolus

The onset of action is generally half an hour to one hour after administration of a single intrathecal dose of baclofen. Peak spasmolytic effect is seen at approximately 4 hours after dosing, the effect lasting 4 to 8 hours. Onset, peak response and duration of action may vary with individual patients depending on the severity of symptoms and the dose, method and speed of drug administration.

Distribution

After single intrathecal bolus injection/short-term infusion of baclofen, the volume of distribution, calculated from CSF concentrations, ranges from 22 to 157 mL. The concentrations of baclofen in plasma and the CSF after intrathecal bolus injection and intrathecal infusion have been investigated in three separate studies and the results are depicted in the table below.

Mode of Administration	Dose	Patient No	V_d (L)	Plasma (ng/mL)	CSF (ng/mL)
Bolus Infusion	100-600 µg 50-1200 µg/24h	14 14	- -	5-20 0-5	- 130-950
Bolus Infusion	75-137 µg 83-210 µg/24h	4 4	0.05-0.16 -	- -	- 132-1240

Bolus Infusion	50-100 µg 96-600 µg/24h	7 10	0.02-0.15 -	- -	- 76-1240

According to the half-life measured in the CSF, steady-state CSF concentrations will be reached within 1-2 days. No data are available for paediatric patients.

There is inadequate information available on the distribution of the two enantiomers.

Elimination

The pharmacokinetics of Cerebrospinal Fluid (CSF) clearance of baclofen, calculated from intrathecal bolus or continuous infusion studies, approximate CSF turnover, suggesting elimination is by bulk-flow removal of CSF. After both single bolus injection and chronic lumbar subarachnoid infusion using an implantable pump system, the mean CSF clearance is about 30 mL/h.

The elimination half-life in the CSF after single intrathecal bolus injection/short-term infusion of 50 to 136 micrograms baclofen ranges from 1 to 5 hours. The elimination half-life of baclofen in the CSF at steady-state has not been determined.

Special populations

Elderly Patients

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 elimination but a similar systemic exposure to baclofen compared to young adults. However, the extrapolation of these results to multi-dose treatment suggests no significant pharmacokinetics difference between young adults and elderly patients.

Paediatrics

In paediatric patients, respective plasma concentrations are at or below 10 ng/mL.

Hepatic impairment

No pharmacokinetic data is available in patients with hepatic impairment after administration of Lioresal Intrathecal. However, as 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 majorly eliminated unchanged through the kidneys, accumulation of unchanged drug in patients with renal impairment cannot be excluded.

5.3 Preclinical safety data

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.

Genotoxicity

Baclofen was negative for mutagenic and genotoxic potential in tests in bacteria, mammalian cells, yeast, and Chinese hamsters. The evidence suggests that baclofen is unlikely to have mutagenic potential.

Carcinogenicity

A two year carcinogenicity study in rats (oral administration) found no evidence that baclofen had carcinogenicity potential at oral doses up to 100 mg/kg/day. An apparently dose-related increase in the incidence of ovarian cysts and of enlarged and/or haemorrhagic adrenals at the highest two doses (50 and 100 mg/kg/day) was observed in female rats. The clinical relevance of these findings is not known.

Ovarian cysts have been found by palpation in about 5% of the multiple sclerosis patients who were treated with oral baclofen for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are known to occur spontaneously in a proportion of the normal female population.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: sodium chloride; water for injections.

6.2 Incompatibilities

Lioresal ampoules for intrathecal administration should not be mixed with other infusion or injection solutions. Glucose solutions are incompatible due to a chemical reaction with baclofen.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Storage: Protect from heat (Store below 30°C).

6.5 Nature and contents of container

Colourless type I glass ampoule; in packs of 1.

6.6 Special precautions for disposal and other handling

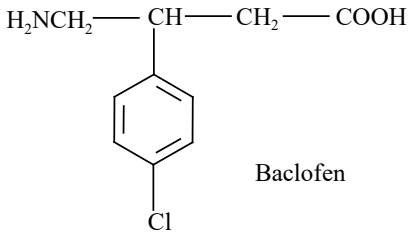
Lioresal Intrathecal is intended for intrathecal injection. Each ampoule is intended for single use only. Discard any unused portion. Do not freeze. Do not heat-sterilise.

Dilution instructions

For patients who require concentrations other than 0.05 mg/mL, Lioresal Intrathecal must be diluted, under aseptic conditions, with sterile **preservative-free sodium chloride for injection**.

6.7 Physicochemical properties

The active ingredient of Lioresal Intrathecal is baclofen ((RS)-4-amino-3-(4-chlorophenyl)butanoic acid). The chemical structure of baclofen (CAS number: 1134-47-0) is:



Baclofen

Baclofen is a chemical analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Novartis New Zealand Limited

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9. DATE OF FIRST APPROVAL

30 July 2015

10. DATE OF REVISION OF THE TEXT

20 December 2023

SUMMARY OF CHANGES

Section	Summary of Changes
4.4	Add tachycardia as symptom of withdrawal, modify wording for patients with history of peptic ulcers.
4.5	Modify interaction with anti-hypertensives.
4.8	Add hypersensitivity to post-market ADR with frequency 'Not known'; editorial revision to correct the system organ classes (SOC) for existing ADR.
4.9	Add tachycardia and tinnitus as a symptom of overdose.

(Internal document code: lrsi220224iNZ based on CDS 31 October 2023)