AUSTRALIAN PRODUCT INFORMATION- LIORESAL® INTRATHECAL (BACLOFEN)

1. NAME OF THE MEDICINE

Baclofen.

2. QUALITIATIVE AND QUANTITATIVE

Lioresal Intrathecal contains ampoules of 50 microgram of baclofen per 1 mL (0.05 mg/mL), 10 mg baclofen per 20 mL (0.5 mg/mL) or 10 mg baclofen per 5 mL (2 mg/mL).

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

3. PHARMACEUTICAL FORM

Lioresal Intrathecal is a solution for intrathecal injection and intrathecal infusion. It is a clear, colourless solution.

Lioresal Intrathecal does not contain 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

Lioresal Intrathecal is intended for administration in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, in implantable pumps suitable for continuous administration of baclofen solution into the intrathecal space.

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 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 by experienced clinicians

in properly equipped centres in order to minimise the risks in the perioperative phase (see Section 4.4 Special warnings and precautions for use).

Intrathecal administration of baclofen through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience. Specific instructions for implanting, programming and/or refilling the implantable pump are given by the pump manufacturers, and must be strictly adhered to.

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 the 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.

To determine the initial total daily dose of intrathecal baclofen 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.

<u>Patients with spasticity of spinal origin</u>

After the first 24 hours, the dosage should be adjusted slowly on a daily basis to achieve the desired clinical effect, with dosage increments limited to 10 - 30% to avoid possible overdosing.

<u>Patients with spasticity of cerebral origin</u>

After the first 24 hours, the dosage should be adjusted slowly on a daily basis to achieve the desired clinical effect, with dosage increments limited to 5 - 15% to avoid possible overdosing.

With programmable pumps, the dose should be increased only once every 24 h. 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 substantially increased and no clinical effect is achieved, check for proper pump function and catheter patency.

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

Maintenance therapy

The clinical goal is to maintain muscle tone as close to normal as possible and to minimise the frequency and severity of spasms without inducing intolerable side effects, or to titrate the dose to the desired degree of muscle tone for optimal function when patients with cerebral spasticity are treated. The lowest dose producing an adequate response should be used.

Patients with spasticity of spinal origin

The daily dose may be gradually increased in steps of 10 - 30% to maintain adequate symptom control by adjusting the dosing rate of the pump and/or the concentration of baclofen in the reservoir. The daily dose may also be reduced by 10 - 20% if patients experience side effects.

Patients with spasticity of cerebral origin

The daily dose may be gradually increased by 5 - 20%, but no more than 20%, to maintain adequate symptom control by adjusting the dosing rate of the pump and/or the concentration of baclofen in the reservoir. The daily dose may also be reduced by 10 - 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.

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.

Maintenance dosage for long-term continuous infusion of intrathecal baclofen in patients with spasticity of spinal origin ranges from 10 micrograms /day to 1200 micrograms /day, most patients being adequately maintained on 300 - 800 micrograms/day.

In patients with spasticity of cerebral origin, the maintenance dosage for long-term continuous infusion of intrathecal baclofen ranges from 22 micrograms/day to 1400 micrograms/day, with a mean daily dose of 276 micrograms/day at 12 months and 307 micrograms/day at 24 months. Paediatric patients under twelve years of age generally require lower dosages than do older patients; the dose ranges from 24 - 1199 micrograms/day, with a mean daily dose of 274 micrograms/day.

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

Delivery regimen

Intrathecal baclofen is most often administered in a continuous infusion mode immediately after pump implantation. However, after the patient has stabilised with regard to daily dose and functional status, and provided the pump allows it, a more complex mode of delivery may be started to optimise control of spasticity at different times of the day. For example, patients who have greater 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.

Development of tolerance

During long-term treatment approximately 5% of patients become refractory to increasing doses. There is not sufficient experience to make firm recommendations for management of tolerance. After a few days cessation of baclofen the sensitivity to baclofen may be restored. Treatment should be resumed at the initial continuous infusion dose, followed by a titration phase to avoid accidental overdose. This must be performed in a hospital unit. (also see Section 4.4. Special warnings and precautions for use - Abrupt Discontinuation or Withdrawal of Lioresal Intrathecal Therapy (including associated with catheter or device malfunction). Caution should be exercised when switching from Lioresal Intrathecal to morphine and vice versa (see Section 4.5 Interactions with other medicines and other forms of interactions).

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 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).

Instructions for Use / Handling

Ampoule specifications

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

Lioresal Intrathecal contains no preservatives.

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

Lioresal ampoules containing 10 mg/5 mL and 10 mg/20 mL are available for use with infusion pumps. The concentration chosen for use depends upon the total daily dose required as well as the delivery rate of the pump. Please consult the pump manufacturer's manual for specific recommendations.

Dilution instructions

For patients who require concentrations other than 0.05 mg/mL, 0.5 mg/mL or 2 mg/mL, Lioresal Intrathecal must be diluted, under aseptic conditions, with sterile **preservative-free**

sodium chloride for injection.

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.

Pump specifications

Evidence demonstrating the efficacy of Lioresal Intrathecal was obtained in randomised, controlled investigations conducted by Medtronic, Inc., using the Medtronic SynchroMed® Infusion System Model 8610 and 8611H. Additional experience was gained with the Infusaid® 400 Infusion System. These devices are implantable drug delivery systems with refillable reservoirs, which are implanted in a subcutaneous pocket usually on the abdominal wall. The devices are connected to an intrathecal catheter which passes subcutaneously to the subarachnoid space.

Use of Lioresal Intrathecal is recommended only with implantable pumps that have been approved for intrathecal use by the Therapeutic Devices Evaluation Committee and the Therapeutic Goods Administration.

Stability of Lioresal Intrathecal in the infusion pump

Lioresal Intrathecal was tested and found to be stable in the implanted Medtronic-SynchroMed® Infusion System Model 8610 and 8611H for 11 weeks and in the Infusaid® 400 Infusion System for 28 days. Baclofen may be used with subsequent models that the pump manufacturer specifies to be compatible with Lioresal Intrathecal and which have been approved for intrathecal use by the Therapeutic Devices Evaluation Committee and the Therapeutic Goods Administration. Parenteral drug products should be inspected for particulate matter and discolouration prior to administration whenever solution and container permit.

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

Abrupt Discontinuation or Withdrawal of Lioresal Intrathecal Therapy (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.

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 Lioresal Intrathecal.

Common reasons for abrupt interruption of intrathecal baclofen therapy included malfunction of the catheter (especially disconnection), low volume in the pump reservoir and device malfunction and end of pump battery life. Device malfunction resulting in altered drug delivery leading to withdrawal symptoms including death has been reported. Human error may have played a causal or contributing role in some cases. Prevention of abrupt discontinuation of intrathecal baclofen 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 baclofen withdrawal (e.g. priapism).

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 intrathecal baclofen). Consult the technical manual of the implantable infusion system for additional post-implant clinician and patient information.

Safety considerations during use

It is mandatory that the patient, the physicians responsible for the patient, and all those involved in the care of the patient receive adequate information about the risks of this mode of treatment. Physicians must be adequately trained in chronic intrathecal infusion therapy. Everyone concerned with the treatment and care of the patient should be instructed on the signs and symptoms of overdose, procedures to be followed in the event of overdose, and proper home care of the pump and insertion site.

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).

Screening phase

The 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.

Pump implantation and use

Intrathecal administration of Lioresal through an implanted delivery system should only be undertaken by physicians with the necessary knowledge and experience in properly equipped centres in order to minimise the risks in the perioperative period. Specific instructions for implanting, programming and/or refilling the implantable pump are given by the pump manufacturers, and must be strictly adhered to.

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. A local infection or catheter malplacement can also lead to drug delivery failure, which may result in sudden Lioresal Intrathecal withdrawal and its related symptoms (see Section 4.4. Special warnings and precautions for use - Abrupt Discontinuation or Withdrawal of Lioresal Intrathecal Therapy (including associated catheter or device malfunction).

Reservoir refilling

Reservoir refilling must be performed by qualified and fully trained personnel following the directions provided by the pump manufacturer. Strictly aseptic filling is required to avoid microbial contamination and serious infection.

Refill intervals should be carefully calculated to prevent depletion of the reservoir, as this would result in the return of severe spasticity or potentially life-threatening symptoms of withdrawal (see Section 4.4. Special warnings and precautions for use - Abrupt Discontinuation or Withdrawal of Lioresal Intrathecal Therapy (including associated with catheter or device malfunction).

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.

Patient monitoring after pump implantation

Following surgical implantation of the pump, particularly during the initial phases of 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 reasonably stable. A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir.

Inflammatory mass at the tip of the implanted catheter

Cases of inflammatory mass at the tip of the implanted catheter that can result in serious neurological impairment, including paralysis, have been reported with Lioresal intrathecal. Studies in animal models have demonstrated that the intrathecal infusion of some opioids can readily induce formation of an inflammatory mass, especially with high doses and/or high concentrations. However, limited experimental data in dogs suggest that intrathecal baclofen as a sole agent does not induce an inflammatory mass. The most frequent symptoms associated with inflammatory mass are: 1) 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), 2) pain, 3) neurological deficit/dysfunction. Clinicians should monitor patients on intraspinal therapy carefully for any new neurological signs or symptoms. Clinicians should use their medical judgement regarding the most appropriate monitoring specific to their patients' medical needs to identify prodromal signs and symptoms for inflammatory mass especially if using pharmacy compounded drugs or admixtures that include opioids. 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 not unlike the symptoms experienced by patients with severe spasticity from their disease. In some cases, performance of an imaging procedure may be appropriate to confirm or rule-out the diagnosis of an inflammatory mass.

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 Lioresal Intrathecal.

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.

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 clinical worsening, suicidal behaviour or thoughts, or unusual changes in behaviour and seek medical advice immediately if these symptoms present (see Section 4.8 Adverse effects (Undesirable effects).

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.

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 Special warnings and precautions for use - Abrupt Discontinuation or Withdrawal of Lioresal Intrathecal Therapy (including associated with catheter or device malfunction).

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

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 a history of peptic ulcers and based on observations after oral baclofen therapy, in those with pre-existing sphincter hypertonia, impaired renal function. In rare instances elevations of aspartate aminotransferase (AST), alkaline phosphatase and glucose in the serum have been recorded when using oral baclofen.

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.

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

Several patients over the age of 65 years have been treated with intrathecal baclofen during the clinical trials without specific problems. 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. However, as doses are individually titrated, there is not likely to be a particular problem in treating elderly patients.

Paediatric patients (below 18 years)

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. 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.

Effects on laboratory tests

No data available.

4.5. Interactions with other medicines and other forms of interactions

There is inadequate systematic experience with the use of intrathecal baclofen in combination with other medications to predict specific drug-drug interactions.

Anticipated interactions resulting in concomitant use not being recommended

Levodopa/DDC (DOPA decarboxylase) 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. Therefore, in patients with Parkinson's disease receiving treatment with baclofen and levodopa plus DDC inhibitor (e.g. carbidopa), adverse events, such as mental confusion, hallucinations and agitation may occur. Thus, caution should be exercised when intrathecal Lioresal is administered to patients receiving levodopa/DDC inhibitor therapy.

Observed interactions to be considered

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.

Anticipated interactions to be considered

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

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.

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.

Antihypertensives

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

4.6. Fertility, pregnancy and lactation

Effects on fertility

There are no data available on the effect of baclofen on fertility in humans,

Use in pregnancy (Category B3)

Risk summary

There are 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 5.2 Pharmacokinetic 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.

Animal data

In two teratogenic studies in pregnant rats, baclofen has been shown to increase the incidence of omphalocoeles (ventral hernias) in fetuses, at a dose of 20 mg/kg/day, which is maternotoxic. The relevance of this finding to humans is unknown. At the same dose there was also an increased incidence of incomplete sternebral ossification in the fetuses.

In mice, no teratogenic effects were observed at a dose of 81.5 mg/kg/day given via the diet or up to 40 mg/kg/day given by gavage. At 40 mg/kg/day by gavage, a delay in fetal growth was associated with maternal anorexia. The lack of maternotoxicity seen in the dietary study suggests that the dose used was inadequate.

Likewise, maternally given oral doses, up to 10 mg/kg/day to pregnant rabbits, were devoid of

teratogenic effects. Maternotoxicity was manifested as a sedative effect. Skeletal examination of fetuses revealed a marked increase in the absence of ossification of the phalangeal nuclei of fore-limbs and hind-limbs.

Use in lactation

In lactating mothers taking **oral** baclofen in therapeutic doses, the active substance passes into the milk, but in quantities so small that no undesirable effects on the infant are to be expected.

It is not known if detectable levels of drug are present in the milk of nursing mothers receiving intrathecal baclofen.

4.7. Effects on ability to drive or 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. Adverse effects (Undesirable effects)

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

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	**N = 153**	**N = 150**
	Screening[a]	Titration[b]	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)
Tremour	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)

A causal link between events observed and the administration of baclofen cannot be reliably assessed in many cases, since many of the adverse events reported are known to occur in association with the underlying conditions being treated. Nevertheless, some of the more commonly reported reactions - drowsiness / somnolence, dizziness, headache, nausea, hypotension, hypotonia - appear to be drug-related.

Adverse events in patients with spasticity of spinal or cerebral origin

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.

Adverse events are listed by MedDRA system organ class. The corresponding frequency category 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 and confusion
Uncommon	suicidal ideation, attempted suicide (see Section 4.4. Special warnings and precautions for use), hallucinations, paranoia/paranoic reaction, euphoria
Nervous system disorders	
Very common	drowsiness/somnolence.
Common	sedation, dizziness/light-headedness, seizures, headache, paraesthesiae, slurred speech, lethargy, fatigue, difficulty concentrating, disorientation.
Uncommon	nystagmus, decreased coordination/ataxia, memory loss/impairment, dysphoria, cerebrovascular disorders.
	Seizures and headache occur more often in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.
Eye disorders	
Common	accommodation disorders, blurred vision, double vision
Cardiac disorders	
Uncommon	bradycardia
Vascular disorders	
Common	hypotension.
Uncommon	hypertension, , deep vein thrombosis, skin flushing, paleness, collapse.
Respiratory, thoracic and mediastinal disorders	
Common	respiratory depression, dyspnoea, bradypnoea, feeling of pressure in the chest (chest tightness), pneumonia.
Gastrointestinal tract	
Common	nausea/vomiting, constipation, dry mouth, diarrhoea, decreased appetite, increased salivation.
Uncommon	ileus, dysphagia, decreased taste sensation.
	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 oedema, peripheral oedema (swelling of lower

	extremities).
Uncommon:	alopecia, diaphoresis.
Renal and urinary disorders	
Common	urinary incontinence, urinary retention, (sluggish bladder, bladder spasm).
	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	muscular weakness/hypotonia, disturbances of gait and balance.
Common	muscular hypertonia.
Reproduction system	
Common	sexual dysfunction.
General disorders and administration site conditions	
Common	pain, asthenia, fever, chills.
Uncommon:	hypothermia, septicemia, subdural haemorrhage, accidental injury, weight loss
Rare	life-threatening withdrawal symptoms due to drug delivery failure (see Section 4.4. Special warnings and precautions for use Abrupt Discontinuation or Withdrawal of Lioresal Intrathecal Therapy).

Adverse events associated with the delivery system

Inflammatory mass at the tip of the catheter, dislodgement/kink/rupture of the catheter with possible complications, infection of place of implantation, meningitis, septicemia, pump-pocket seroma and haematoma (potential risk of inflammation), pump malfunction and CSF leakages and skin ulcers after quite some time, and overdosage or underdosage due to wrong manipulation of the device have been reported, whereby in some cases a causal relationship with baclofen cannot be excluded. Device malfunction resulting in altered drug delivery leading to withdrawal symptoms including death has been reported (see Section 4.4. Special warnings and precautions for use).

Adverse drug reaction 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 were 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.

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

Reproductive system: erectile dysfunction.

Immune system disorders: hypersensitivity

Reporting of suspected adverse effects

Reporting suspected adverse reaction after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse drug reactions at www.tga.gov.au/reporting-problems.

4.9. Overdosage

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.

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 intrathecal baclofen overdose (coma) were reported in a sensitive adult patient after receiving a 25 microgram intrathecal bolus dose.

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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, the clinical effects of baclofen take the form of a beneficial action on reflex muscle contractions and of marked relief from painful spasm, automatism and clonus.

Baclofen improves patient mobility and facilitates physiotherapy. Consequent important gains include 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 GABAB 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.

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

Clinical trials

<u>Spasticity of spinal origin</u>

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

The following kinetic parameters must be interpreted in the light of intrathecal administration coupled with slow CSF circulation.

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.

Continuous infusion: Baclofen's antispasmodic action is first seen 6 to 8 hours after initiation of continuous infusion. Maximum efficacy is observed within 24 to 48 hours.

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	100-600 μg	14	-	5-20	-
Infusion	50-1200 μg /24h	14	-	0-5	130-950
Bolus	75-137 μg	4	0.05-0.16	-	-
Infusion	83-210 μg /24h	4	-	-	132-1240
Bolus	50-100 μg	7	0.02-0.15	-	-
	96-600 μg /24h	10	-	-	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.

At steady-state conditions during continuous intrathecal infusion, a baclofen concentration gradient is built up in the range between 1.8:1 and 8.7:1 (mean: 4:1) from lumbar to cisternal CSF. 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 great. This is of clinical importance insofar as spasticity in the lower extremities can be effectively treated with little effect on the upper limbs and with fewer CNS adverse reactions resulting from effects on the brain centres.

During intrathecal infusion plasma concentrations do not exceed 5 ng/mL, confirming that baclofen passes only slowly across the blood-brain barrier. In paediatric patients, respective plasma concentrations are at or below 10 ng/mL.

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

Excretion

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

5.3 Preclinical safety data

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 did not induce mutations in bacterial or mammalian cells in vitro, lacked DNA damaging activity in the sister chromatid exchange assay, and had no clastogenic activity in

the nuclear anomaly test.

Carcinogenicity

A two year carcinogenicity study in rats 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

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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precaution for storage

Protect from heat (store below 30ºC). Medicines should be kept out of the reach of children.

6.5 Nature and contents of container

0.05 mg baclofen per 1 mL ampoule; packs of 1.

10 mg baclofen per 20 mL ampoule (0.5 mg/mL); packs of 1.

10 mg baclofen per 5 mL ampoule (2 mg/mL); packs of 1.

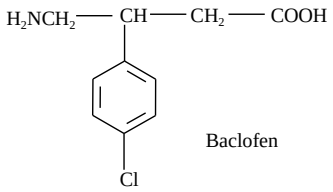
6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physiochemical properties

Chemical structure

The active ingredient of Lioresal Intrathecal is β-(Aminomethyl)-p-chlorohydrocinnamic acid (= baclofen), a racemic mixture of the R, (-) and S, (+) isomers. The chemical structure of baclofen is:



Baclofen

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

CAS number: 1134-47-0.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Medicine (Schedule 4).

8. SPONSOR

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9. DATE OF FIRST APPROVAL

19 March 1996.

10. DATE OF REVISION

22 February 2024.

Summary table of changes

Section changed	Summary of new information
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 system organ classes (SOC) and correct assignment of existing ADR.
4.9	Add tachycardia and tinnitus as a symptom of overdose.