Intrathecal Baclofen Therapy: Determining Appropriate Utilization in Patients With Severe Spasticity Related to Multiple Sclerosis

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Introduction

Spasticity—a condition characterized by muscle stiffness, tightening, or spasm with associated involuntary jerking, pain, and weakness—may be associated with stroke, spinal cord injury, multiple sclerosis (MS), cerebral palsy, or brain injury. Spasticity can be a significant impediment to functioning. Severe spasticity can interfere significantly with patients’ quality of life and daily activities, as well as their emotional well-being. As described in one study, “Spasticity is not just an inconvenience; it can be devastating and incapacitating.”

Spasticity, to some degree, develops in more than 70% of MS patients, many of whom also experience painful and disabling muscle spasms. In the North American Research Committee on MS (NARCOMS) study, MS patients were found to be especially susceptible to spasticity as the disease progresses; patients with higher levels of spasticity had MS longer, with more relapses and worsening symptoms.

Poorly managed spasticity can lead to contractures. Contracture prevention or early identification and treatment are critical to avoid long-term complications such as pressure sores. Spasticity should be managed according to the level of severity (ie, mild, moderate, or severe) and degree that it interferes with the patient’s comfort, care, needs, or function. Medical treatments include the use of oral antispasticity medication, botulinum toxin, phenol, or intrathecal baclofen. Medtronic ITB Therapy (intrathecal baclofen therapy) is indicated for patients with severe spasticity. For those with spasticity of spinal origin, they should have demonstrated inadequate effect or intolerable side effects from oral baclofen. Patients whose spasticity results from traumatic brain injury should wait at least one year before beginning ITB Therapy.

This supplement focuses on MS spasticity and the safe and effective use of ITB Therapy in the management and the treatment of severe spasticity.

What Is ITB Therapy?

ITB Therapy delivers a liquid form of baclofen, called Lioresal Intrathecal (baclofen injection), directly into the intrathecal space, where fluid flows around the spinal cord. ITB Therapy relieves severe spasticity by delivering Lioresal Intrathecal via a programmable pump that is surgically placed and connected to a catheter in the body.

ITB Therapy uses the implantable SynchroMed II drug infusion system. The Medtronic SynchroMed II pump is completely programmable, so medication administration is personalized to each patient’s specific needs. The pump can be programmed to deliver a wide...
range of infusion rates and offers a variable pattern to optimize dosing for patients whose drug requirements change over the course of a day, or over the course of a week. Integral to the system is a handheld external programmer that the physician uses to adjust the dose and infusion rates.

**Patient Selection—Who Is a Candidate for ITB Therapy?**

Candidates for ITB Therapy are patients who continue to experience severe spasticity despite having tried standard therapies.¹ According to guidelines from the Consortium of Multiple Sclerosis Centers, treatment for patients with unrelenting spasticity should begin with range-of-motion exercise, stretching, and strengthening programs, along with sequentially prescribed oral medications, starting with oral baclofen or tizanidine.¹ If oral baclofen is not effective or well tolerated, patients should be considered for ITB Therapy.¹

There are other considerations for ITB Therapy candidates. Patients’ mobility should be assessed: the Expanded Disability Status Scale (EDSS) can be used to classify patients with MS and spasticity into 3 levels of mobility impairment—ambulatory, ambulatory with assistance, and non-ambulatory.¹ Patients in the middle group, ambulatory with assistance, may rely on the use of extensor spasticity for transfers and ambulation. If so, the relative benefits of decreased spasticity should be weighed against the possibility of reduced functional mobility.¹

Further, patients should be screened for their willingness and ability to visit a clinic or center regularly for pump refills and adjustments.¹ Noncompliance with scheduled management appointments can result in suboptimal effect, or more seriously, baclofen withdrawal from pump reservoir depletion.¹ Abrupt withdrawal may result in high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity; in rare cases, rhabdomyolysis, multiple organ failure, and death have followed.¹ The medically deleterious consequences of sudden discontinuation can be avoided by careful attention to programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Thorough education of patients and caregivers must stress the importance of keeping scheduled refill visits and watching for the early symptoms of baclofen withdrawal. Special attention should be given to patients at risk (eg, spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or intrathecal baclofen).⁶

Additionally, patients must understand that they will need to monitor their response to treatment, possible complications with dose changes, and interactions with alcohol and other prescription medications. Patients and their families must know how the pump may affect other technology. For example, it may set off metal detectors at security checkpoints; patients should carry their ITB Therapy identification card.⁸

MRI can safely be performed on a patient with a Synchromed II infusion system.⁸ In horizontal, closed-bore MRI scanners 3.0 Tesla or less, the pump will stop drug infusion for the duration of the MRI procedure and will automatically resume normal functioning afterward. Precautions must be taken by the MRI technician. Medtronic offers a 24-hour support department that can be reached at 800-707-0933. Written technical information that can be faxed to radiology departments is also available.⁸

A contraindication for administration of intrathecal baclofen for a patient with severe spasticity is hypersensitivity to baclofen. Implantation of the infusion system is contraindicated if the patient’s body size is too small, if the patient needs a pump implant deeper than 2.5 cm, or has spinal anomalies or active infection.⁷ The following are not necessarily contraindications to ITB Therapy: a history of seizures; the presence of another device, such as a ventriculoperitoneal shunt or pacemaker; prior soft-tissue lengthening procedures, tendon releases; or selective posterior rhizotomy.

**Timing of Therapy**

Prior to pump implantation and initiation of ITB Therapy, all candidates must show a positive clinical response to a bolus dose administered intrathecally by lumbar puncture in a screening trial.¹ The screening trial can offer helpful data about future dose, re-
sponse patterns, and possible functional outcomes, all of which may be used in monitoring treatment after the pump is implanted. The procedure is usually performed in an outpatient setting, but must be conducted in a medically supervised and adequately equipped environment, and resuscitative equipment should be available.

Before the test, patients should be informed that they may experience a temporary decrease in function when their spasticity is abruptly withdrawn. Patients should know, also, that their degree of test response does not correlate with their anticipated level of change in tone once the pump is implanted and adjusted. This is because of differences in response between the large test bolus as opposed to controlled delivery through the pump. It is important that patients know that the dose will be changed over several months in order to determine the most effective dose.

Prior to the screening trial, the patient should be tapered from anticoagulation medications, if necessary; oral antispasticity medications need not be tapered.

An intrathecal baclofen screening trial involves administration of a 50 mcg bolus into the intrathecal space. The patient is observed and evaluated over the next 4 to 8 hours. If the initial response is less than desired, a second bolus injection of 75 mcg may be administered 24 hours after the first. If the response remains inadequate, a final bolus screening dose of 100 mcg may be given 24 hours later. Generally, the medication begins to take effect within 2 hours, peaks at about 4 hours, and then wears off, until the patient returns to baseline after approximately 8 hours. Adverse events that may occur with the screening procedure are hypotonia, somnolence, nausea, vomiting, headache, and dizziness. The test is contraindicated in the presence of infection.

A positive response consists of a significant decrease in muscle tone and/or frequency and/or severity of spasms. This means a decrease of 1 to 2 points in the modified Ashworth score and/or a reduction of 2 points in the spasm frequency scale.

Most patients can go home after 8 hours without difficulty and should be able to resume oral antispasmodic drugs later that evening. Patients should be advised to avoid strenuous activities for a few days, to drink plenty of fluids, and to lie flat if they have a spinal headache.

Clinical Trial Findings Supporting the Benefit of ITB Therapy

In patients with severe spasticity related to MS and spinal cord injury, ITB Therapy has been efficacious, safe, and well tolerated. Its benefits have been shown in a number of trials.

ITB Therapy reduced spasms and spasticity in 97% of patients during a pre-implant screening test; of the 66 patients, 33 had MS and 32 had spinal trauma. Sixty-four patients experienced a reduction in Ashworth and/or spasm frequency scale scores of ≥2 points. To maintain the Ashworth and spasm scale scores, the baclofen dose was increased gradually during the first 2 years, after which it tended to stabilize. The most frequent drug-related adverse events were drowsiness, dizziness, blurred vision, and slurred speech. Catheter system repair was needed in just over one-half of the patients. The study authors noted that ITB Therapy was well tolerated; transient side effects in some patients were easily treated by lowering the dosage. The authors concluded that long-term control of spinal spasticity by intrathecal baclofen can be achieved in most patients.

In an early trial of ITB Therapy, Coffey et al reported that severe spasticity of spinal origin responded “dramatically” to long-term ITB Therapy. Of 93 patients with severe spasticity of spinal origin, 59 had spinal cord injury, 31 had MS, and 3 had other spinal pathology; 75 had pump implantation. At last follow-up (mean follow-up, 19 months), the mean Ashworth scale score had decreased from 3.9 (pre-operative) to 1.7, and the mean spasm frequency score decreased from 3.1 to 1.0. The daily dose of ITB Therapy needed to maintain a therapeutic effect increased. The dose at the beginning and at the end of the study tended to be higher for patients with spinal cord injury than for patients with MS. Complications and side effects seen in this study included three deaths unrelated to therapy, 31 device-related complications resolved by a secondary surgery or invasive procedure, and 11 patients experienced reversible drug-related complications, including respi-
ratory depression, hypotension, temporary weakness, seizure, hypertension, depression, and drowsiness.10

Middel and colleagues studied health-related quality of life (QoL), health status measures, and costs in patients with severe spasticity caused by MS or spinal cord injury.11 In this double-blind, randomized trial, 22 patients were recruited from 9 Dutch hospitals; 59% had MS.11 Questionnaires were administered at the study’s beginning, at 4 and 13 weeks after the start of the placebo-controlled phase, and at 26 and 52 weeks of the follow-up phase.11

ITB Therapy resulted in a significant improvement in self-reported, health-related QoL in the areas of recreation and pastimes, rest and sleep, mobility, body care and movement, as evaluated by the sickness impact profile.11 Additionally, the changes between the initial and final scores on the physical health dimension and the overall scores of the sickness impact profile and the Hopkins symptom checklist indicated improvement.11 The group that received baclofen immediately after implantation showed significant improvement in clinical outcome measures.11 This group demonstrated significant changes in the appropriate physical and psychosocial dimensions of self-reported health status.11

Ordia et al evaluated 152 patients (63 had MS) with severe spasticity of spinal cord origin for ITB Therapy; 131 patients underwent implant surgery, and all but one patient responded positively to the ITB bolus dose.3 Patients experienced a significant reduction in degree of spasticity: the mean Ashworth score decreased from 4.2 preoperatively to 1.3 on chronic intrathecal baclofen, and the spasm score decreased from a mean of 3.4 to 0.6.3 Activities of daily living, such as moving from chair to bed, became easier.3 With ITB Therapy and fewer or no oral medications, most patients felt less fatigued, more alert, and better able to concentrate.3 Eighteen ambulatory patients experienced improved gait and balance, and 2 patients who had been non-ambulatory were able to walk.3 A number of patients, who now had better spasticity control, were able to work or to take less sick time.3 To maintain effective spasticity control, patients required a steady increase in dose, especially during the first 6 months of ITB Therapy.3 At 12 months, the dose was stable for spinal cord injury patients but continued to increase for MS patients, possibly resulting from disease fluctuation or progression.3 Drug-related complications included constipation, muscular hypotonia, headache, urinary retention, erectile dysfunction, nausea, dizziness, drowsiness, hypotension, bradycardia, and tolerance to baclofen.3 Catheter-related problems included occlusions, breaks, punctures, and dislodgments.3 Procedure-related complications included superficial pump pocket infection, pocket erosion, cerebrospinal fluid leak, post-spinal puncture headache, and meningitis.3

ITB Therapy was studied in 138 patients, who were enrolled in 24 European centers, with intractable spasticity.12 The patients, 30 of whom had MS, experienced significant improvements in muscle tone in both lower and upper extremities, as well as significant decreases in spasm scores.12 The patients in this study also reported reduced pain, improved function, and increased treatment satisfaction.12 More than 60% of patients and their physicians described spasticity and pain relief after the start of ITB Therapy as good or very good.12 Physicians
reported good or very good levels of overall satisfaction with ITB Therapy for almost 90% of their patients. Changes in dosage were needed in more than 90% of patients to maximize the therapeutic effect. This high rate stresses the importance of using a programmable pump, as in this study, to allow noninvasive adjustment of baclofen flow rate at any time during therapy. About 43% of patients reported adverse events, mostly related to patients’ underlying condition, the device implant surgery, or catheter complications.

Vender et al, who surveyed 35 MS patients after ITB Therapy implantation, found that they experienced no complications related to the implant procedure, and excellent longevity and long-term efficacy of the pump system. The chief advantage of ITB Therapy in this survey was associated with the ability of 75% of patients to discontinue oral medication. The most striking clinical response to ITB Therapy was improvement in spontaneous and/or sensory-motor triggered spasms; these dropped from 44.5% before ITB Therapy to 21% after therapy. Patient satisfaction was high, and most would recommend the device to others. No adverse responses were noted, although 2 patients declined an implant due to what they described as an overresponse, and 1 patient requested removal of the pump because she did not feel a benefit.

Adverse effects resulting from ITB Therapy may be device-related or drug-related. The most frequent drug adverse effects vary by indication but include hypotonia (34.7%), somnolence (20.9%), headache (10.7%), convulsion (10.0%), dizziness (8.0%), urinary retention (8.0%), nausea (7.3%), and paresthesia (6.7%). Pump system component failures leading to pump stall are rare but may lead to withdrawal. Dosing or reprogramming errors may result in clinically significant overdose or undertose. Acute massive overdose may result in coma and may be life-threatening. The most frequent and serious adverse effects related to device and implant procedures are catheter dislodgement from the intrathecal space, catheter break/cut, and implant site infection, including meningitis.

**Ongoing Monitoring and Management**

Monitoring ITB Therapy requires a broad clinical reach, extending to knowledge and assessment of the patient’s health, emotional status, and treatments that influence severe spasticity.

Achieving correct dose titration and successful patient management requires the careful attention of a knowledgeable clinical team, which can include a neurologist, a physiatrist, or a clinician trained in ITB Therapy to monitor dose adjustments and clinical status. Rehabilitation specialists can extend the benefits of ITB Therapy with training exercises, which improve functional status. Rehabilitation encompasses traditional therapies, as well as hydrotherapy, hippotherapy, and yoga.

After implant, frequent visits may be needed during the titration phase, which is defined as the time to reach a steady dose for 4 to 6 weeks. During these visits, the dose may be adjusted, therapy effects assessed, oral medications tapered, and rehabilitation services started. However, the titration process may last months, depending on the patient’s diagnosis and sensitivity to dosing changes. Patients with progressive disease, such as MS, may need more time, perhaps as long as 6 to 9 months, to reach an appropriate dose. Ambulatory patients, who may be more sensitive to rate increases, may allow only a 3% to 6% increase in the total daily dose. During the maintenance phase, it is essential to individualize each patient’s optimum ITB therapy dose for reducing muscle tone and spasms, maximizing function, and avoiding side effects. Once the maintenance dose has been determined, infusion modes can be programmed. Programmable infusion modes can be a significant advantage of ITB Therapy. Increased delivery of the drug can be provided for managing nighttime- or care-related spasms. Conversely, decreased drug delivery can be provided to allow for use of spasticity in transfers or ambulation. With flexible dosing, individualization can be done for work and weekend schedules, and other events and activities.

Additionally, processes should be established to provide assessment of the pump and the catheter system when necessary and to deal with pump-related emergency care and other issues associated with the patient’s condition.
Overcoming Barriers to Treatment With ITB Therapy

ITB Therapy was approved by the U.S. Food and Drug Administration in 1992 to treat severe spasticity of spinal origin, and in 1996 to treat severe spasticity of cerebral origin. ITB Therapy should be considered for MS patients with severe spasticity at all stages of the disease when they cannot tolerate or have an insufficient response to oral baclofen. A specialist with spasticity management expertise beyond oral medications should be consulted earlier in the disease process, ideally when the EDSS score nears 4.0, rather than ≥6.5, which has been more often used as a decision point.

In a study based on NARCOMS data, patients were asked, among other questions, how they learned about ITB Therapy. Among the group taking oral medications, 65% knew about the pump, but only 24% of this number had heard about it from their physicians. Given that 26.4% of patients in the oral medication group reported severe or total spasticity, it is possible that there may be candidates for ITB Therapy in this group. Further, about 33% of the respondents, overall, reported their level of spasticity as moderate or worse, even though they were taking single and multiple drugs. It is possible that some of these patients could be candidates for ITB Therapy.

According to most ITB Therapy group patients in this study, their physicians had recommended the treatment because they considered it a more effective treatment for a high level of spasticity, ease of dose regulation, and acceptable risk of side effects. Although fear of surgery may be a barrier, the percentage of patients in the NARCOMS study who were not comfortable with a surgical procedure was the same in both ITB Therapy and oral medication groups. Clearly, patients were able to overcome any hesitancy about undergoing the procedure.

According to the study authors, the results suggest that the treatment of spasticity in MS patients may frequently be suboptimal. Erwin et al concluded the following: “The principal barrier to the use of ITB Therapy in MS patients appears to be the failure of physicians to present ITB as an effective and well tolerated therapeutic option to many patients who would be suitable candidates.” Additionally, physicians may not know how to choose suitable candidates or understand the effect of severe spasticity on QoL. Finally, the fact that only ~50% of MS centers have inclusive spasticity management programs may be an impediment to greater knowledge and use of ITB Therapy. Underappreciation of the impact of spasticity on quality of life, concerns regarding potential treatment complications, and lack of treatment advocacy by MS clinicians have resulted in underutilization of a safe and effective treatment option.

References


For more information and links to online resources, please see the digital version of this supplement at www.neurologyreviews.com

Please refer to the accompanying full prescribing information and system information for details or call Medtronic at 1-800-328-0810.
## RESOURCES

### Physician Finder
How to find a specialist with ITB Therapy expertise and tips for selecting the right physician

[MORE](#) Click here to search for an ITB Therapy specialist.

### Videos

#### Bob's Story
Bob struggles with severe spasticity due to MS. In this video he shares his experience with ITB Therapy.

[MORE](#) Click here to view Bob's story.

#### ITB Therapy Screening Test: Adult Patient
This video educates adult patients, families, and caregivers on the ITB Therapy screening test.

[MORE](#) Click here to watch screening test video.

### Education and Training
Educational video programs for clinicians who treat severe spasticity. These videos include topics such as how to educate patients on ITB Therapy, and assessing patients for overall spasticity management.

[MORE](#) Click here for educational and training videos for health care providers.

### Consensus Paper

**Intrathecal Baclofen in Multiple Sclerosis: Too Little, Too Late?**
Originally published online ahead of print January 31, 2011, by *Multiple Sclerosis Journal*, this article summarizes the findings and recommendations of an expert panel on the use of ITB Therapy in the MS population and the role of the physician and comprehensive care team in patient selection, screening, and management.

[MORE](#) Click here to read the consensus paper.

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Please refer to the accompanying full prescribing information and system information for details or call Medtronic at 1-800-328-0810.
SynchroMed® II Drug Infusion System Brief Summary:

Product technical manuals and the appropriate drug labeling must be reviewed prior to use for detailed disclosure.

Indications:
US: Chronic intraspinal (epidural and intrathecal) infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain, chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain, and chronic intrathecal infusion of Lioresal™ Intrathecal (baclofen injection) for the management of severe spasticity; chronic intravascular infusion of flouxuridine (FUDR) or methotrexate for the treatment of primary or metastatic cancer. Outside of US: Chronic infusion of drugs or fluids tested as compatible and listed in the product labeling.

Contraindications:
Infection; implant depth greater than 2.5 cm below skin; insufficient body size; spinal anomalies; drugs with preservatives, drug contraindications, drug formulations with pH ≤3, use of catheter access port (CAP) kit for refills or of refill kit for catheter access, blood sampling through CAP in vascular applications, use of Personal Therapy Manager to administer opioid to opioid-naïve patients or to administer ziconotide.

Warnings:
Non-indicated formulations may contain neurotoxic preservatives, antimicrobials, or antioxidants, or may be incompatible with and damage the system. Failure to comply with all product instructions, including use of drugs or fluids not indicated for use with system, or of questionable sterility or quality, or use of non-Medtronic components or inappropriate kits, can result in improper use, technical errors, increased risks to patient, tissue damage, damage to the system requiring revision or replacement, and/or change in therapy, and may result in additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug under- or overdose. Refer to appropriate drug labeling for indications, contraindications, warnings, precautions, dosage and administration information, screening procedures and underdose and overdose symptoms and methods of management. Physicians must be familiar with the drug stability information in the product technical manuals and must understand the dose relationship to drug concentration and pump flow rate before prescribing pump infusion. Implantation and ongoing system management must be performed by individuals trained in the operation and handling of the infusion system. An inflammatory mass that can result in serious neurological impairment, including paralysis, may occur at the tip of the implanted catheter. Clinicians should monitor patients on intraspinal therapy carefully for any new neurological signs or symptoms, change in underlying symptoms, or need for rapid dose escalation.

Inform patients of the signs and symptoms of drug under- or overdose, appropriate drug warnings and precautions regarding drug interactions, potential side effects, and signs and symptoms that require medical attention, including prodromal signs and symptoms of inflammatory mass. Failure to recognize signs and symptoms and seek appropriate medical intervention can result in serious injury or death. Instruct patients to notify their healthcare professionals of the implanted pump before medical tests/procedures, to return for refills at prescribed times, to carry their Medtronic device identification card, to avoid using shortwave (RF) diathermy within 30 cm of the pump or catheter. Effects of other types of diathermy (microwave, ultrasonic, etc.) on the pump are unknown. Drug infusion is suspended during MRI; for patients who can not safely tolerate suspension, use alternative drug delivery method during MRI. Patients receiving intrathecal baclofen therapy are at higher risk for adverse events, as baclofen withdrawal can lead to a life threatening condition if not treated promptly and effectively. Confirm pump status before and after MRI. Reference product labeling for information on sources of EMI, effects on patient and system, and steps to reduce risks from EMI.

Precautions:
Monitor patients after device or catheter replacement for signs of underdose/overdose. Infuse preservative-free (intraspinal) saline or, for vascular applications, infuse heparinized solutions therapy at minimum flow rate if therapy is discontinued for an extended period of time to avoid system damage. EMI may interfere with programmer telemetry during pump programming sessions. EMI from the SynchroMed programmer may interfere with other active implanted devices (e.g., pacemaker, defibrillator, neurostimulator).

Adverse Events:
Include, but are not limited to, spinal/vascular procedure risks; infection; bleeding; tissue damage, damage to the system or loss of, or change in, therapy that may result in additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug underdose or overdose, due to end of device service life, failure of the catheter, pump or other system component, pump inversion, technical/programming errors, or improper use, including use of non-indicated formulations and/or not using drugs or system in accordance with labeling; pocket seroma, hematoma, erosion, infection; post-lumbar puncture (spinal headache); CSF leak and rare central nervous system pressure-related problems; hygroma; radiculitis; arachnoiditis; spinal cord bleeding/damage; meningitis; neurological impairment (including paralysis) due to inflammatory mass; potential serious adverse effects from catheter fragments in intrathecal space, including potential to compromise antibiotic effectiveness for CSF infection; anesthesia complications; body rejection phenomena; local and systemic drug toxicity and related side effects; potential serious adverse effects from catheter placement in intravascular applications.

USA Rx Only  Rev 0311
LIORESAL® INTRATECHAL (baclofen injection)

Abrupt discontinuation of intrathecal baclofen, regardless of the cause, has resulted in sequelae that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhomboimobility, multiple organ-system failure and death. Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to 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. 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 postimplantation clinician and patient information (see WARNINGS).

DESCRIPTION

LIORESAL INTRATECHAL (baclofen injection) is a muscle relaxant and antispastic. Its chemical name is 4- amino-3-(4-chlorophenyl)butanoic acid, and its structural formula is:

\[ \text{H}_2\text{N-CH-CH}_2\text{COOH} \]

Baclofen is a white to off-white, odorless or practically odorless crystalline powder, with a molecular weight of 213.66. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform.

LIORESAL INTRATECHAL is a sterile, pyrogen-free, isotonic solution free of antioxidants, preservatives or other potentially neurotoxic additives indicated only for intrathecal administration. The drug is stable in solution at 37°C and compatible with CSF. Each milliliter of LIORESAL INTRATECHAL contains baclofen U. S. P. 50 mcg, 100 mcg or 2000 mcg and sodium chloride 9 mg in Water for Injection, pH range is 5.0 - 7.0. Each ampule is intended for SINGLE USE ONLY. Discard unused portion. DO NOT AUTOCLAVE

CLINICAL PHARMACOLOGY

The precise mechanism of action of baclofen as a muscle relaxant and antispasticity agent is not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals; although actions at supraspinal sites may also occur and contribute to its clinical effect. Baclofen is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and may exert its effects by stimulation of the GABA, receptor subtype.

LIORESAL INTRATECHAL when introduced directly into the intrathecal space permits effective CSF concentrations to be achieved with resultant plasma concentrations 100 times less than those occurring with oral administration. In people, as well as in animals, baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

Pharmacodynamics of LIORESAL INTRATECHAL:

Intrathecal Bolus:

Adult Patients: The onset of action is generally one-half hour to one hour after an intrathecal bolus. Peak spasmolytic effect is seen at approximately four hours after dosing and effects may last four to eight hours. Onset, peak effects and duration of action may vary with individual patient and/or by the dose and severity of symptoms.

Pediatric Patients: The onset, peak response and duration of action is similar to those seen in adult patients.

Continuous Infusion:

LIORESAL INTRATECHAL’s antispastic action is first seen at 6 to 8 hours after initiation of continuous infusion. Maximum activity is observed in 24 to 48 hours.

Continuous Infusion: No additional information is available for pediatric patients.

Pharmacokinetics of LIORESAL INTRATECHAL:

The peak plasma concentration of LIORESAL INTRATECHAL calculated from intrathecal bolus or continuous infusion studies approximately CSF turnover, suggesting elimination is by bulk flow removal of CSF.

Intrathecal Bolus: After a bolus lumbar injection of 50 or 100 mcg LIORESAL INTRATECHAL in seven patients, the average CSF elimination half-life was 1.51 hours over the first four hours and the average CSF clearance was approximately 38 ml/hour.

Continuous Infusion: The mean CSF clearance for LIORESAL INTRATECHAL (baclofen injection) was approximately 30 ml/hour in a study involving ten patients on continuous intrathecal infusion. Concurrent plasma concentrations of baclofen during intrathecal administration are expected to be low (< 5 ng/ml).

Limited pharmacodynamic data suggest that a lumbar-ostial concentration gradient of about 4:1 is established along the neuraxis during baclofen infusion. This is based upon simultaneous CSF sampling via ostial and lumbar tap in 5 patients receiving continuous baclofen infusion at the lumbar level at doses associated with therapeutic efficacy; the interpatient variability was great. The gradient was not altered by position.

Six pediatric patients (age 8-18 years) receiving continuous intrathecal baclofen infusion at doses of 77-400 mcg/day had plasma baclofen levels near or below 10 ng/ml.

INDICATIONS

LIORESAL INTRATECHAL is indicated for use in the management of severe spasticity. Patients should first respond to a screening dose of intrathecal baclofen prior to consideration for long-term infusion via an implantable pump. For spasticity of spinal cord origin, chronic infusion of LIORESAL INTRATECHAL via an implantable pump should be reserved for patients unresponsive to oral baclofen therapy, or those who experience intolerable CNS side effects at effective doses. Patients with spasticity due to traumatic brain injury should wait at least one year after the injury before consideration of long term intrathecal baclofen therapy. LIORESAL INTRATECHAL (baclofen injection) is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only in implantable pumps approved by the FDA specifically for the administration of LIORESAL INTRATECHAL into the intrathecal space.

Spasticity of Spinal Cord Origin: Evidence supporting the efficacy of LIORESAL INTRATECHAL was obtained in randomized, controlled investigations that compared the effects of either a single intrathecal dose or a three day intrathecal infusion of LIORESAL INTRATECHAL to placebo in patients with severe spasticity and spams due to either spinal cord trauma or multiple sclerosis. LIORESAL INTRATECHAL 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 INTRATECHAL 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 randomized controlled cross-over trial of 51 patients with cerebral palsy, provided strong, statistically significant results; LIORESAL INTRATECHAL was superior to placebo in reducing spasticity as measured by the Ashworth Scale. A second cross-over 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 = .0666) and provided directionally favorable results. The last study, however, did not provide data that could be reliably analyzed.

LIORESAL INTRATECHAL therapy may be considered an alternative to destructive neurosurgical procedures. Prior to implantation of a device for chronic intrathecal infusion of LIORESAL INTRATECHAL, patients must show a response to LIORESAL INTRATECHAL in a screening trial (see Dosage and Administration).

CONTRAINDICATIONS

Hypersensitivity to baclofen. LIORESAL INTRATECHAL is not recommended for intravenous, intramuscular, subcutaneous or epidural administration.

WARNINGS

LIORESAL INTRATECHAL is for use in single bolus intrathecal injections (via a catheter placed in the lumbar intrathecal space or injection by lumbar puncture) and in implantable pumps approved by the FDA specifically for the intrathecal administration of baclofen. Because of the possibility of potentially life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure, physicians must be adequately trained and educated in chronic intrathecal infusion therapy.

The pump system should not be implanted until the patient’s response to bolus LIORESAL INTRATECHAL injection is adequately evaluated. Evaluation (consisting of a screening procedure: see Dosage and Administration) requires that LIORESAL INTRATECHAL be administered into the intrathecal space via a catheter or lumbar puncture. Because of the risks associated with the screening procedure and the adjustment of dosage following pump implantation, these phases must be conducted in a medically supervised and adequately equipped environment following the instructions outlined in the Dosage and Administration sections.

Resuscitative equipment should be available.

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

It is mandatory that the patient, all patient caregivers, and the physician responsible for the patient receive adequate information regarding the risks of this mode of treatment. All medical personnel and caregivers should be instructed in: 1) the signs and symptoms of overdose, 2) procedures to be followed in the event of overdose and 3) proper home care of the pump and insertion site.

Overdose: Signs of overdosage may appear sudden or insidious. Acute massive overdose may present as coma. Less sudden and/or less severe forms of overdose may present with signs of drowsiness, light-headedness, dizziness, somnolence, respiratory depression, seizures, nystagmus, hypertension and loss of consciousness progressing to coma. Should overdose appear likely, the patient should be taken immediately to a hospital for assessment and emptying of the pump reservoir. In cases reported to date, overdose has generally been related to pump malfunction or dosing error (See Drug Overdose Symptoms and Treatment).

Extreme caution must be used when filling an FDA approved implantable pump. Such pumps should only be filled through the reservoir refill septum. However, some pumps are also equipped with a catheter access port that allows direct access to the intrathecal catheter. Direct injection into this catheter access port may cause a life-threatening overdose.

Withdrawal: Abrupt withdrawal of intrathecal baclofen, regardless of the cause, has resulted in sequelae that included high fever, altered mental status, exaggerated rebound spasticity and muscle rigidity that in rare cases progressed to rhomboimobility, multiple organ-system failure, and death. In the first few years of post-marketing experience, 27 cases of withdrawal temporarily 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. Common reasons for abrupt interruption of intrathecal baclofen therapy included malfunction of the
catheter (especially disconnection), low volume in the pump reservoir, and end of pump battery life; human error may have played a causal or contributing role in some cases. Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to 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.

All patients receiving intrathecal baclofen therapy are potentially at risk for withdrawal symptoms. Early symptoms of baclofen withdrawal may include return of baseline spasticity, pruritus, hypotension, and paresthesias. 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 rhadopathy.

Rapid pump disconnection 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 agonists such as oral or enteral baclofen, or oral, enteral, or intravenous benzodiazepines may potentially prevent fatal sequelae. Oral or enteral baclofen alone should not be relied upon for the resolution of intrathecal baclofen withdrawal.

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

**Spasticity of Spinal Cord Origin:** There were three deaths occurring among the 211 patients treated with LIROSAL INTRATECHAL in pre-marketing studies as of March 1996. These deaths were not attributed to the therapy.

**Screening:** Patients should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Please consult pump manufacturer's manual for specific recommendations. Safety and effectiveness in pediatric patients below the age of 4 have not been established.

**Screening:** Patients should be infection-free prior to the screening trial with LIROSAL INTRATECHAL (baclofen injection) because the presence of a systemic infection may interfere with the assessment of the patient’s response to bolus LIROSAL INTRATECHAL.

**Pump Implantation:** Patients should be infection-free prior to pump implantation because the presence of infection may increase the risk of surgical complications. Moreover, a systemic infection may complicate dosing.

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

Reservoir refilling must be performed by trained and qualified personnel following the directions provided by the pump manufacturer. Refill intervals should be carefully calculated to prevent depletion of the reservoir, as this would result in the cessation of continuous therapy and possibly withdrawal symptoms.

**Spinal Cord Physiology and Pain:** Strict aseptic technique in filling is required to avoid bacterial contamination and serious infection. A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir.

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

Additional considerations pertaining to dosage adjustment: It may be important to titrate the dose to maintain some degree of muscle tone and allow occasional spasms to (1) help promote circulatory function, (2) prevent the formation of deep vein thrombosis, (3) optimize activities of daily living, and ease of care.

Except in overdose related emergencies, the dose of LIROSAL INTRATECHAL should be proportionately reduced if the drug is discontinued for any reason.

An attempt should be made to discontinue constant oral antispasmodic medication to avoid possible overdose or adverse drug interactions, either prior to screening or following implant and initiation of chronic LIROSAL INTRATECHAL infusion. Reduction and discontinuation of oral antispasmodics should be done slowly and with careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispasmodics should be avoided.

**Drowsiness:** Drowsiness has been reported in patients on LIROSAL INTRATECHAL. Patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system depressant effects of LIROSAL INTRATECHAL (baclofen injection) may be additive to those of alcohol and other CNS depressants.

**Precautions in special patient populations:** Careful dose titration of LIROSAL INTRATECHAL is needed when spasticity is necessary to sustain upright posture and balance in locomotion or whenever spasticity is used to obtain optimal function and care.

Patients suffering from psychiatric disorders, schizophrenia, or confusional states should be treated cautiously with LIROSAL INTRATECHAL and kept under careful surveillance, because exacerbations of these conditions have been observed with oral administration.

LIROSAL INTRATECHAL should be used with caution in patients with a history of autonomic dys-reflexia. The presence of nociceptive stimuli or abrupt withdrawal of LIROSAL INTRATECHAL (baclofen injection) may cause an autonomic dysreflexic episode.

Because LIROSAL is primarily excreted unchanged by the kidneys, it should be given with caution in patients with impaired renal function and it may be necessary to reduce the dosage.

**Laboratory Tests:** No specific laboratory tests are deemed essential for the management of patients on LIROSAL INTRATECHAL.

**Drug Interactions:** There is inadequate systematic experience with the use of LIROSAL INTRATECHAL in combination with other medications to predict specific drug-drug interactions. Interactions attributed to the combined use of LIROSAL INTRATECHAL and epidural morphine include hypertension and dyspnea.

**Cardiovascular, Myocardial, and Impairment of Fertility:**

No increase in tumors was seen in rats receiving LIROSAL INTRATECHAL (baclofen USP) orally for two years at approximately 30-60 times on a mg/kg basis, or 10-20 times on a mg/m² basis, the maximum oral dose recommended for human use. Mutagenicity assays with LIROSAL INTRATECHAL have not been performed.

**Pregnancy Category C:** LIROSAL INTRATECHAL (baclofen USP) given orally has been shown to increase the incidence of omphalocle (ventral hernia) in fetuses of rats given approximately 13 times on a mg/kg basis, or 3 times on a mg/m² basis, the maximum oral dose recommended for human use; this dose also caused reductions in food intake and weight gain in the dams. This abnormality was not seen in mice or rabbits. There are no adequate and well-controlled studies in pregnant women: LIROSAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** In mothers treated with oral LIROSAL INTRATECHAL (baclofen USP), the therapeutic active substance passes into the breast milk. It is not known whether detectable levels of drug are present in breast milk of nursing mothers receiving LIROSAL INTRATECHAL. As a general rule, nursing should be undertaken while a patient is receiving LIROSAL INTRATECHAL only if the potential benefit justifies the potential risks to the infant.

**Pediatric Use:**

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Please consult pump manufacturer’s manual for specific recommendations. Safety and effectiveness in pediatric patients below the age of 4 have not been established.

Considereations based on experience with oral LIROSAL (baclofen USP)

A decrease in incidence of oivain cysts was observed in female rats treated chronically with oral LIROSAL. Ovarian cysts have been foud by palpation in about 4 of the multiple sclerosis patients who were treated with oral LIROSAL for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population.

**ADVERSE DRUG EVENTS**

**Spasticity of Spinal Cord Origin:**

Commonly Observed in Patients with Spasticity of Spinal Origin — In pre- and post-marketing clinical trials, the most commonly observed adverse events associated with use of LIROSAL INTRATECHAL (baclofen injection) which were not seen at an equivalent incidence in placebo-treated patients were: somnolence, dizziness, nausea, hypotension, headache, convulsions, and hypotension.

Associated with Discontinuation of Treatment — 8/474 patients with spasticity of spinal cord origin receiving long term infusion of LIROSAL INTRATECHAL in pre- and post-marketing clinical studies in the U.S. discontinued treatment due to adverse events. These include pump pocket infections (3), meningitis (2), wound dehiscence (1), gyneceological infections (1) and pump overpressure (1) with unknown if, any, sequel. Eleven patients who developed coma secondary to overdose had their treatment temporarily suspended, but all were subsequently re-started and were not, therefore, considered to be true discontinuations.

Fatal Events — Two were reported.

Incidence in Controlled Trials — Experience with LIROSAL INTRATECHAL (baclofen injection) obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimating the incidence of adverse events because the studies were of very brief duration (up to three days of infusion) and involved only a total of 63 patients. The following events occurred among the 31 patients receiving LIROSAL INTRATECHAL (baclofen injection) in two studies: hypotension (5), dizziness (5), headache (3), hypotension (1), drowsiness (1), and respiratory depression (1). The incidence of the experience, a causal linkage between events observed and the administration of LIROSAL INTRATECHAL cannot be reliably assessed in many cases and many of the adverse events reported are known to occur in association with the underlying conditions being treated. Nonetheless, many of the adverse events commonly reported reactions — hypotension, somnolence, dizziness, paresthesia, nausea, vomiting, and headache — may be associated with clearly drug-related events.

Adverse experiences reported during all U.S. studies (both controlled and uncontrolled) are shown in the following table. Eight of 474 patients who received chronic infusion via implanted pumps had adverse experiences which led to discontinuation of long term treatment in the pre- and post-marketing studies.

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

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Percent of Patients Reporting Events</th>
<th>N = 376</th>
<th>N = 474</th>
<th>N = 432</th>
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<tr>
<td></td>
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<td>Titration‡</td>
<td>Maintenance§</td>
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<tr>
<td>Hypotonia</td>
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<td>1.5</td>
<td>25.3</td>
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<tr>
<td>Somnolence</td>
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<td>6.7</td>
<td></td>
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<td>Nausea and Vomiting</td>
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<td>2.3</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
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<td>1.0</td>
<td>5.1</td>
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<td>4.7</td>
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</tr>
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<td>0.6</td>
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<tr>
<td>Urinary Incontinence</td>
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<tr>
<td>Insomnia</td>
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<td>1.6</td>
<td></td>
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<td>0.9</td>
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<tr>
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<tr>
<td>Dryness</td>
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<td>1.2</td>
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<tr>
<td>Fever</td>
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<td>0.2</td>
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<tr>
<td>Urinary Frequency</td>
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<td>0.9</td>
<td></td>
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<tr>
<td>Dysuria</td>
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<tr>
<td>Polyuria</td>
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<td>0.5</td>
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<tr>
<td>Hypertension</td>
<td>0.2</td>
<td>0.6</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

† Following administration of test bolus
‡ Two month period following implant
§ Beyond two months following implant
N = total number of patients; † ‡ § each period
%–% of patients evaluated

In addition to the more common (1% or more) adverse events reported in the prospectively followed 576 domestic patients in pre- and post- marketing studies, experience from an additional 194 patients exposed to LIROSAL INTRATHecal (baclofen injection) from foreign studies has been reported. The following adverse events, not described in the table, and arranged in decreasing order of frequency, and classified by body system, were reported:

- **Nervous System:** Abnormal gait, thinking abnormal, tremor, amnesia, twitching, vasodilatation, cerebrovascular accident, nystagmus, personality disorder, psychotic depression, cerebral ischemia, emotional lability, euphoria, hypotonia, febrile drug dependence, incoordination, paranoid reaction and paresis.

- **Diseases ofDigestive System:** Flatulence, dysphagia, dyspepsia and gastritis.

- **Cardiovascular:** Postural hypotension, bradycardia, palpitations, syncope, arrhythmia ventricular, deep thirombophlebitis, pallor and tachycardia.

- **Respiratory:** Respiratory disorder, aspiration pneumonia, hyperventilation, pulmonary embolus and hemits.

- **Urogenital:** Hematuria and kidney failure.

- **Skin:** Alopea and sweating.

- **Metabolic and Nutritional Disorders:** Weight loss, albuminuria, dehydration and hyperglycemia.

- **Special Sensation:** Abnormal vision, abnormality of accommodation, photophobia, taste loss and tinnitus.

- **Body as a Whole:** Suicide, lack of drug effect, abdominal pain, hypothermia, neck rigidity, chest pain, chills, face edema, flu syndrome and overdose.

- **Hemic and Lymphatic System:** Anemia.

**Spasticity of Cerebral Origin:**

- **Commonly Observed** — In pre-marketing clinical trials, the most commonly observed adverse events associated with use of LIROSAL INTRATHecal (baclofen injection) which were not seen at an equivalent incidence among placebo-treated patients included agitation, constipation, somnolence, leukocytosis, chills, urinary retention and hypotonia.

- **Associated with Discontinuation of Treatment** — Nine of 211 patients receiving LIROSAL INTRATHecal in pre-marketing clinical studies in the U.S. discontinued long term infusion due to adverse events associated with intrathecal therapy.

- **The nine adverse events leading to discontinuation were infection (3), CSF leaks (2), meningitis (2), drainage (1), and unmanageable trunk control (1).**

- **Fatalities** — Three deaths, none of which were attributed to LIROSAL INTRATHecal, were reported in patients in clinical trials involving patients with spasticity of cerebral origin. See Warnings on other deaths reported in spinal spasticity patients.

- **Incidence in Controlled Trials** — Experience with LIROSAL INTRATHecal (baclofen injection) obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimating the incidence of adverse events because the studies involved a total of 62 patients exposed to a single 50 mcg intrathecal bolus. The following events occurred among the 62 patients receiving LIROSAL INTRATHecal in two randomized, placebo-controlled trials involving cerebral palsy and head injury patients, respectively: agitation, constipation, somnolence, leukocytosis, nausea, vomiting, nystagmus, chills, urinary retention, and hypotonia.

- **Events Observed during the Pre-marketing Evaluation of LIROSAL INTRATHecal** — Adverse events associated with the use of LIROSAL INTRATHecal reflect experience gained with a total of 211 U.S. patients with spasticity of cerebral origin, of whom 112 were pediatric patients (under age 16 at enrollment). They received LIROSAL INTRATHecal for periods of one day (screening) (N= 211) to 84 months (maintenance) (N= 1). The usual screening bolus dose administered prior to pump implantation in these studies was 50 – 75 mcg. The maintenance dose ranged from 22 mcg to 1400 mcg per day. Doses used in this patient population for long term infusion are generally lower than those required for patients with spasticity of spinal cord origin.

- **Because of the open, uncontrolled nature of the experience, a causal linkage between events observed and the administration of LIROSAL INTRATHecal cannot be reliably assessed in many cases. Nonetheless, many of the more commonly reported reactions — somnolence, dizziness, headache, nausea, hypotension, hypotonia and coma — appear clearly drug-related.**

- **The most frequent (≥1%) adverse events reported during all clinical trials are shown in the following table. Nine patients discontinued long term treatment due to adverse events.**
<table>
<thead>
<tr>
<th>Percent of Patients Reporting Events</th>
<th>N = 115</th>
<th>N = 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening*</td>
<td>2.4</td>
<td>2.0</td>
</tr>
<tr>
<td>Titration*</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Maintenance*</td>
<td>2.0</td>
<td>1.0</td>
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<tr>
<td><strong>Adverse Event</strong></td>
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</tr>
<tr>
<td>Hypotension</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.4</td>
<td>1.0</td>
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<tr>
<td>Headache</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Nasoan and Vomiting</td>
<td>1.0</td>
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</tr>
<tr>
<td>Vomiting</td>
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<td>1.0</td>
</tr>
<tr>
<td>Urinary Retention</td>
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<td>0.5</td>
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<td>Convulsions</td>
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<td>0.5</td>
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</tr>
<tr>
<td>Urinary Incontinence</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>Urination Impaired</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* Following administration of test bolus

| Two month period following implant

| Beyond two months following implant

| N= Total number of patients: existence each period: 211 patients received drug, (1 of 21) received placebo only.

The more common (1% or more) adverse events reported in the prospectively followed 211 patients exposed to Lioresal Intrathecal (baclofen) injection have been reported. In the total cohort, the following adverse events, not described in the table, and arranged in decreasing order of frequency, and classified by body system, were reported:

- **Central Nervous System:** Akathisia, ataxia, confusion, depression, ophthophobia, amnesia, anxiety, hallucinations, hysteria, insomnia, dysthymia, personality disorders, reflexes decreased, and vasodilatation.

- **Digestive System:** Dysphagia, fecal incontinence, gastrointestinal hemorrhage and tongue disorder.

- **Cardiovascular:** Bradycardia.

- **Respiratory:** Apnea, dyspnea and hyperventilation.

- **Urogenital:** Abnormal ejaculation, kidney calculus, oliguria and varicities.

- **Skin and Appendages:** Rash, sweating, alopecia, contact dermatitis and skin ulcer.

- **Special Senses:** Abnormal accommodation.

- **Body as a Whole:** Death, fever, abdominal pain, carcinoma, malaise and hypotension.

**Hemic and Lymphatic System:** Leukocytosis and petechial rash.

### Drug Overdose

Special attention must be given to recognizing the signs and symptoms of overdosage, especially during the initial screening and dose- titration phase of treatment, but also during reintroduction of Lioresal Intrathecal after a period of interruption in therapy.

**Symptoms of Lioresal Intrathecal Overdose:** Drowsiness, light-headedness, dizziness, somnolence, respiratory depression, seizures, rotational progression of hypotonia and loss of co-ordinated progression to coma of up to 72 hr duration. In most cases reported, coma was reversible without sequelae after drug was discontinued. Symptoms of Lioresal Intrathecal overdose were reported in a sensitive adult patient after receiving a 25 mg intrathecal bolus.

**Treatment Suggestions for Overdose:**

There is no specific antidote for treating overdoses of Lioresal Intrathecal (baclofen injection); however, the following steps should ordinarily be undertaken:

1. Residual Lioresal Intrathecal solution should be removed from the pump as soon as possible.
2. Patients with respiratory depression should be intubated if necessary, and the drug is eliminated.

### Ancillary reports

Reports indicate that intravenous physostigmine may reverse central side effects, notably drowsiness and respiratory depression. Caution in administering physostigmine is advised, however, because its use has been associated with the induction of seizures and bradycardia.

**Physostigmine Doses for Adult Patients:** Administer 2 mg of physostigmine intramuscularly or intravenously at a slow controlled rate of no more than 1 mg per minute. Dosage may be repeated if life-threatening signs, such as arrhythmia, loss of consciousness, occur.

**Physostigmine Doses for Pediatric Patients:** Administer 0.02 mg/kg physostigmine intramuscularly or intravenously, do not give more than 0.5 mg per minute. The dosage may be repeated at 5 to 10 minute intervals until a therapeutic effect is obtained or a maximum dose of 2 mg is attained.

Physostigmine may not be effective in reversing large overdoses and patients may need to be maintained with respiratory support.

If lumbar puncture is not contraindicated, consideration should be given to withdrawing 10-40 mL of CSF to reduce CSF baclofen concentration.

### Dosage Administration

Refer to the manufacturer's manual for the implantable pump approved for intrathecal infusion for specific instructions and precautions for programming the pump and/or refilling the reservoir. There are various pumps with varying reservoir volumes and there are various refill kits available. It is important to be familiar with all of these products in order to select the appropriate refill kit for the particular pump in use.

**Screening Phase:** Prior to pump implantation and initiation of chronic infusion of Lioresal Intrathecal (baclofen injection), patients must demonstrate a positive clinical response to a Lioresal Intrathecal bolus dose administered intrathecally in a screening trial. The screening trial employs Lioresal Intrathecal at a concentration of 50 mg/ml. A 1 ml ampule (50 mg/ml) is available for use in the screening trial. The screening procedure is as follows. An initial bolus containing 50 micrograms in a volume of 1 milliliter is administered into the intrathecal space by barbotage over a period of not less than one minute. The patient is observed over the ensuing 4 to 8 hours. A positive response consists of a significant decrease in muscle tone and/or frequency and/or severity of spasms. If the initial response is less than desired, a second bolus injection may be administered 24 hours after the first. The second screening bolus dose consists of 75 micrograms in 1.5 milliliters. Again, the patient should be observed for an interval of 4 to 8 hours. If the response is still inadequate, a final bolus screening dose of 100 micrograms in 2 milliliters may be administered 24 hours later.

**Pediatric Patients:** The starting screening dose for pediatric patients is the same as in adult patients, i.e., 50 micrograms. However, for very small patients, a screening dose of 25 micrograms may be tried first. Patients who do not respond to a 100 mg intrathecal bolus should not be considered candidates for an implanted pump for chronic infusion.

**Post-Implant Dose Titration Period:** To determine the initial total daily dose of Lioresal Intrathecal, following implant, the screening dose that 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 8 hours, in which case the daily starting dose should be the screening dose delivered over a 24-hour period. No dose increases should be given in the first 24 hours (i.e., until the steady state is achieved).

**Adult Patients with Spasticity of Spinal Cord Origin:** After the first 24 hours, for adult patients, the daily dosage should be increased slowly by 10-30% increments and only once every 24 hours, until the desired clinical effect is achieved.

**Adult Patients with Spasticity of Cerebral Origin:** After the first 24 hours, the daily dose should be increased slowly by 5-15% only once every 24 hours, until the desired clinical effect is achieved. After the first 24 hours, the daily dose should be increased slowly by 5-15% only once every 24 hours, until the desired clinical effect is achieved. If there is no substantive clinical response to increases in the daily dose, check for proper pump function and catheter patency. Patients must be monitored closely for the occurrence of any adverse reactions both during the screening phase and dose- titration period immediately following implant. Resuscitative equipment should be immediately available in case of use in case of hypotension or insensitive side effects.

**Maintenance Therapy:**

- **Spasticity of Spinal Cord Origin Patients:** The clinical goal is to maintain muscle tone as close to normal as possible, and to minimize the frequency and severity of spasms to the extent possible, without inducing intolerable side effects. Very often, the maintenance dose needs to be adjusted during the first few months of therapy while patients adjust to changes in life style due to the alleviation of spasticity. During periodic refills of the pump, the daily dose may be increased by 10-40%, but no more than 40%, to maintain adequate symptom control. The daily dose may be reduced by 10-20% if patients experience side effects. Most patients require gradual increases in dose over time to maintain optimal response during chronic therapy. A sudden large requirement for dose escalation suggests a catheter complication (i.e., catheter kink or dislodgement).
Stability

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

Delivery Specifications

The specific concentration that should be used depends upon the total daily dose required as well as the delivery rate of the pump. LIoresal Intrathecal may require dilution when used with certain implantable pumps. Please consult manufacturer's manual for specific recommendations.

Preparation Instruction:

Screening

Use the 1 ml screening ampule only (50 mcg/ml) for bolus injection into the subarachnoid space. For a 50mcg bolus dose, use 1 ml of the screening ampule. Use 1.5 ml of 50 mcg/ml baclofen injection for a 75 mcg bolus dose.

For the maximum screening dose of 100 mcg, use 2 ml of 50 mcg/ml baclofen injection (2 screening ampules).

Maintenance

For patients who require concentrations other than 500 mcg/ml or 2000 mcg/ml, LIoresal Intrathecal must be diluted.

LIoresal Intrathecal must be diluted with sterile preservative free Sodium Chloride for Injection, USP.

Delivery Regimen:

LIoresal Intrathecal is most often administered in a continuous infusion mode immediately following implant. For those patients implanted with programmable pumps who have achieved relatively satisfactory control on continuous infusion, further benefit may be attained using more complex schedules of LIoresal Intrathecal delivery. For example, patients who have increased spasms 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.

HOW SUPPLIED

LIoresal Intrathecal (baclofen injection) is available in single use ampules of 10 mcg/20 ml (500 mcg/ml) or 10 mcg/ 5 ml (2000 mcg/ml) or 40 mcg/20 ml (2000 mcg/ml) packaged in a Refill Kit for intrathecal administration. For screening, LIoresal Intrathecal is available in a single use ampule of 0.05 mg/1 ml.

Model 8561 LIoresal Intrathecal Refill Kit contains one ampule of 10 mcg/20 ml (500 mcg/ml) (NDC 58281-560-01).

Model 8562 LIoresal Intrathecal Refill Kit contains two ampules of 10 mcg/ 5 ml (2000 mcg/ml) (NDC 58281-561-02).

Model 8563 LIoresal Intrathecal contains one ampule of 0.05 mg/1 ml (NDC 58281-562-01).

Model 8564 LIoresal Intrathecal Refill Kit contains four ampules of 10 mcg/5 ml (2000 mcg/ml) (NDC 58281-561-04) or one ampule of 40 mcg/20 ml (2000 mcg/ml) (NDC 58281-563-01).

Model 8565 LIoresal Intrathecal Refill Kit contains two ampules of 10 mcg/20 ml (500 mcg/ml) (NDC 58281-560-02).

Model 8566 LIoresal Intrathecal Refill Kit contains eight ampules of 10 mcg/ 5 ml (2000 mcg/ml) (NDC 58281-561-08) or two ampules of 40 mcg/20 ml (2000 mcg/ml) (NDC 58281-563-02).

STORAGE

Does not require refrigeration.

Do not store above 86°F (30°C).

Do not freeze.

Do not heat sterilize.

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Medtronic, Inc., Minneapolis, Minnesota 55432-5604 USA.