2020 ANNUAL ASSEMBLY
PRE-ASSEMBLY SESSIONS SPONSOR BOOK

AAPM&R Appreciates Our Supporters of these Pre-Assembly Sessions:

- Utilizing Ultrasound in Your PM&R Practice
- Advancing Clinical Skills in Spasticity Management
- Navigating Opioid Management in a Pandemic

VIRTUAL aaPM&R ANNUAL ASSEMBLY NOVEMBER 8-15, 2020

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TABLE OF CONTENTS

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YOUR PRE-GAME PLAN—
LOG IN EARLY FOR EXCLUSIVE EDUCATION
MONDAY, NOVEMBER 9 - WEDNESDAY, NOVEMBER 11

Education takes center stage at #AAPMR20 and it all starts with our pre-Assembly sessions. Choose from three exciting offerings in the areas of ultrasound, spasticity and pain management—all included with your registration. Attendees will enjoy a virtual learning experience unlike they've ever seen before, led by specialty thought-leaders who will provide real-world, clinically-applicable didactic and interactive case-based discussions on PM&R's hottest topics.

MONDAY, NOVEMBER 9
6-9 PM (CT)

Utilizing Ultrasound in Your PM&R Practice

This session will focus on how ultrasound can be utilized to enhance any musculoskeletal or neuromuscular physiatry practice. Attendees will learn via interactive case-based scenarios. These cases will involve both the upper and lower extremities and will help attendees improve their diagnostic ultrasound skills as well as their ultrasound guided procedural skills. This session is meant to complement the robust STEP Ultrasound Certificate Program curriculum.

Thank you to our virtual exhibitors!

Allergan an AbbVie company · IPSEN Innovation for patient care · KONICA MINOLTA

Partial support for the Utilizing Ultrasound in Your PM&R Practice session has been provided through an educational grant from Allergan, an Abbvie company; Ipsen Biopharmaceuticals, Inc. in compliance with ACCME Standards for Commercial Support.

TUESDAY, NOVEMBER 10
6-9 PM (CT)

Advancing Clinical Skills in Spasticity Management

In this valuable virtual session, you'll learn how to enhance your clinical skills in managing patients with spasticity and related conditions. Attendees will learn via updated journal club round-tables, be presented with case-based scenarios, hear interactive lectures on treatment plans and observe hands-on skills that are relevant to that case scenario. At the end of this session, you'll walk away with new/refreshed and updated evidence-based skills in focal chemodenervation (botulinum toxin, nerve, and motor point blocks) and intrathecal baclofen delivery.

Thank you to our virtual exhibitors!

Allergan an AbbVie company · FLOWONIX · IPSEN Innovation for patient care · Medtronic · Piramal Critical Care · SAOL THERAPEUTICS

Partial support for the Advancing Clinical Skills in Spasticity Management session has been provided through an educational grant from Allergan, an Abbvie company; Ipsen Biopharmaceuticals, Inc.; Merz North America, Inc.; Saol Therapeutics in compliance with ACCME Standards for Commercial Support.

WEDNESDAY, NOVEMBER 11
6-9 PM (CT)

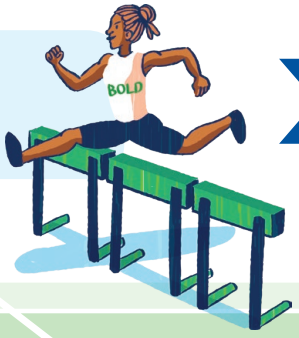
Navigating Opioid Management in a Pandemic

The current opioid crisis and pandemic are two intersecting challenges of opioid management. Physiatrists are at the forefront of treating acute and chronic pain conditions and are frequently asked to manage pain as a method of improving function. Given the current environment and the fluctuating ability to see patients, this session will assist practicing physiatrists in the management of opioid therapy during a pandemic and will provide resources on evidence-based adjuvant treatments options. It is intended to be a real-world, clinically-applicable session that will include didactic presentations, interactive polling and time for participants to ask questions.

Thank you to our virtual exhibitor!

Medtronic · Piramal Critical Care

All pre-Assembly sessions are FREE for registered members and $100 for nonmembers.



Visit **www.aapmr.org/pre-assembly** to learn more.

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BOTOX®
onabotulinumtoxinA injection

BOTOX® SAVINGS PROGRAM

Your eligible patients may

PAY as little as $0*

for BOTOX® treatments

with the BOTOX® Savings Program

Cost of BOTOX® is one of the most common reasons patients decline treatment.[1]

≈ 95% of patients in the BOTOX® Savings Program pay $0[1]

(n = 68,212)

In looking at the largest indication groups in the program, it was shown that enrolling in the BOTOX® Savings Program is one way that can help your patients stay on their BOTOX® treatment.[1,†]

*Restrictions and maximum savings limits apply. Patient out-of-pocket expense may vary. Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state healthcare programs. Please see full terms and conditions herein and at BOTOXSavingsProgram.com. For questions about this program, please call 1-800-44-BOTOX.

†12-month persistency rate from January 2018 to June 2019 for Chronic Migraine, Cervical Dystonia, Adult Upper Limb Spasticity, and Adult Lower Limb Spasticity.

Indications
Bladder Dysfunction:
Overactive Bladder
BOTOX® for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat Cervical Dystonia and spasticity and at lower doses.

Please see additional Indications and Important Safety Information about BOTOX® on following pages.

BOTOX®
onabotulinumtoxinA injection

1 simple offer for every BOTOX® indication

For any BOTOX® indication, patients who enroll may:

- Pay as little as $0 for BOTOX® treatments*
- Save up to $4000 per year*
- Save up to $1500 per treatment*

Comprehensive Reimbursement

Eligible patients are reimbursed for both:

The cost of BOTOX® + The cost of the procedure

Help provide eligible patients with resources for savings on out-of-pocket costs.

Tell patients to enroll by:

Texting **SAVE** to **27747**† • Visiting **BOTOXSavingsProgram.com**

Calling **1-800-44-BOTOX**

*Restrictions and maximum savings limits apply. Patient out-of-pocket expense may vary. Offer not valid for patients enrolled in Medicare, Medicaid, or other federal or state healthcare programs. Please see full terms and conditions herein and at BOTOXSavingsProgram.com. For questions about this program, please call 1-800-44-BOTOX.

†See Privacy and Terms: http://bit.ly/2RvxiWr. Message and data rates may apply. Message frequency may vary. Text HELP for help or STOP to end.

Indications (continued)
Bladder Dysfunction (continued):
Detrusor Overactivity Associated With a Neurologic Condition
BOTOX® is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Chronic Migraine
BOTOX® is indicated for the prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Limitations of Use
Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies.

Adult Spasticity:
Adult Upper Limb Spasticity
BOTOX® is indicated for the treatment of upper limb spasticity in adult patients to decrease the severity of increased muscle tone in elbow, wrist, finger, and thumb flexors (biceps, flexor carpi radialis, flexor carpi ulnaris, flexor digitorum profundus, flexor digitorum sublimis, adductor pollicis, and flexor pollicis longus).

Adult Lower Limb Spasticity
BOTOX® is indicated for the treatment of lower limb spasticity in adult patients to decrease the severity of increased muscle tone in ankle and toe flexors (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus).

Limitations of Use
Safety and effectiveness of BOTOX® have not been established for the treatment of other upper or lower limb muscle groups. BOTOX® has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture.

BOTOX® SAVINGS PROGRAM

Help your patients start and stay on treatment

Of Patients in the BOTOX® Savings Program:

plan to receive BOTOX® again[1]

(n = 107)

considered the program to be an important part of continuing BOTOX®[1]

(n = 107)

Send your commercially insured patients to **BOTOXSavingsProgram.com**.

Indications (continued)
Pediatric Spasticity:
Pediatric Upper Limb Spasticity
BOTOX® is indicated for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age.

Pediatric Lower Limb Spasticity, Excluding Spasticity Caused by Cerebral Palsy
BOTOX® is indicated for the treatment of lower limb spasticity in pediatric patients 2 to 17 years of age, excluding spasticity caused by cerebral palsy.

Cervical Dystonia
BOTOX® is indicated for the treatment of adults with Cervical Dystonia to reduce the severity of abnormal head position and neck pain associated with Cervical Dystonia.

Blepharospasm and Strabismus
BOTOX® is indicated for the treatment of Strabismus and Blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older.

Primary Axillary Hyperhidrosis
BOTOX® is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Limitations of Use
The safety and effectiveness of BOTOX® for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX® for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (eg, hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX® have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

IMPORTANT SAFETY INFORMATION (continued)
CONTRAINDICATIONS
BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation.

BOTOX® is contraindicated for intradetrusor injection in patients with a urinary tract infection; or in patients with urinary retention or post-void residual (PVR) urine volume > 200 mL who are not routinely performing clean intermittent self-catheterization (CIC).

WARNINGS AND PRECAUTIONS
Spread of Toxin Effect
See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX® for Blepharospasm at the recommended dose (30 Units and below), severe primary axillary hyperhidrosis at the recommended dose (100 Units), Strabismus, or for Chronic Migraine at the labeled doses have been reported.

Please see additional Important Safety Information about BOTOX® on following pages.

BOTOX®
onabotulinumtoxinA injection

IMPORTANT SAFETY INFORMATION (continued)
WARNINGS AND PRECAUTIONS (continued)

Lack of Interchangeability Between Botulinum Toxin Products
The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

Serious Adverse Reactions With Unapproved Use
Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX® injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX® to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX®. The safety and effectiveness of BOTOX® for unapproved uses have not been established.

Hypersensitivity Reactions
Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX® should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders
Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BOTOX® (see *Warnings and Precautions*).

Dysphagia and Breathing Difficulties
Treatment with BOTOX® and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing (see *Boxed Warning*).

Pulmonary Effects of BOTOX® in Patients With Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated With a Neurologic Condition
Patients with compromised respiratory status treated with BOTOX® for spasticity or detrusor overactivity associated with a neurologic condition should be monitored closely.

Corneal Exposure and Ulceration in Patients Treated With BOTOX® for Blepharospasm
Reduced blinking from BOTOX® injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders.

Retrobulbar Hemorrhages in Patients Treated With BOTOX® for Strabismus
During the administration of BOTOX® for the treatment of Strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity
Bronchitis was reported more frequently as an adverse reaction in adult patients treated for upper limb spasticity with BOTOX® (3% at 251 Units to 360 Units total dose) compared to placebo (1%). In adult patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX® (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX® (2% at 300 Units to 400 Units total dose) compared to placebo (1%). In pediatric patients treated for upper limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX® (17% at 6 Units/kg and 10% at 3 Units/kg) compared to placebo (9%). In pediatric patients treated for lower limb spasticity, upper respiratory tract infection was not reported with an incidence greater than placebo.

Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity Associated With a Neurologic Condition
Autonomic dysreflexia associated with intradetrusor injections of BOTOX® could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. In clinical trials, the incidence of autonomic dysreflexia was greater in patients treated with BOTOX® 200 Units compared with placebo (1.5% versus 0.4%, respectively).

Urinary Tract Infections in Patients With Overactive Bladder
BOTOX® increases the incidence of urinary tract infection. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX® for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

Urinary Retention in Patients Treated for Bladder Dysfunction
Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post treatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

Overactive Bladder
In clinical trials, 6.5% of patients (36/552) initiated clean intermittent catheterization for urinary retention following treatment with BOTOX® 100 Units as compared to 0.4% of patients (2/542) treated with placebo. The median duration of catheterization for patients treated with BOTOX® 100 Units was 63 days (minimum 1 day to maximum 214 days) as compared to a median duration of 11 days (minimum 3 days to maximum 18 days) for patients receiving placebo.

Patients with diabetes mellitus treated with BOTOX® were more likely to develop urinary retention than nondiabetics. In clinical trials, 12.3% of patients (10/81) with diabetes developed urinary retention following treatment with BOTOX® 100 Units vs 0% of patients (0/69) treated with placebo. In patients without diabetes, 6.3% of patients (33/526) developed urinary retention following treatment with BOTOX® 100 Units vs 0.6% of patients (3/516) treated with placebo.

BOTOX® SAVINGS PROGRAM

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Urinary Retention in Patients Treated for Bladder Dysfunction (continued)

Detrusor Overactivity Associated With a Neurologic Condition

In clinical trials, 30.6% of patients (33/108) who were not using clean intermittent catheterization (CIC) prior to injection, required catheterization for urinary retention following treatment with BOTOX® 200 Units as compared to 6.7% of patients (7/104) treated with placebo. The median duration of postinjection catheterization for these patients treated with BOTOX® 200 Units (n = 33) was 289 days (minimum 1 day to maximum 530 days) as compared to a median duration of 358 days (minimum 2 days to maximum 379 days) for patients receiving placebo (n = 7).

Among patients not using CIC at baseline, those with multiple sclerosis were more likely to require CIC post injection than those with spinal cord injury.

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

ADVERSE REACTIONS

Adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: *Boxed Warning*, *Contraindications*, and *Warnings and Precautions*.

Overactive Bladder

The most frequently reported adverse reactions for overactive bladder occurring within 12 weeks of injection include urinary tract infection (BOTOX® 18%, placebo 6%), dysuria (BOTOX® 9%, placebo 7%), urinary retention (BOTOX® 6%, placebo 0%), bacteriuria (BOTOX® 4%, placebo 2%), and residual urine volume (BOTOX® 3%, placebo 0%).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX® 100 Units and placebo than nondiabetics.

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥ 200 mL following BOTOX® injection compared to those with a maximum PVR < 200 mL following BOTOX® injection, 44% vs 23%, respectively.

Detrusor Overactivity Associated With a Neurologic Condition

The most frequently reported adverse reactions within 12 weeks of BOTOX® injection for detrusor overactivity associated with a neurologic condition include urinary tract infection (BOTOX® 24%, placebo 17%), urinary retention (BOTOX® 17%, placebo 3%), and hematuria (BOTOX® 4%, placebo 3%).

The following adverse event rates were reported at any time following initial injection and prior to reinjection or study exit (median duration of 44 weeks of exposure): urinary tract infections (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX® for Chronic Migraine include neck pain (9%), headache (5%), eyelid ptosis (4%), migraine (4%), muscular weakness (4%), musculoskeletal stiffness (4%), bronchitis (3%), injection-site pain (3%), musculoskeletal pain (3%), myalgia (3%), facial paresis (2%), hypertension (2%), and muscle spasms (2%).

Adult Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® for upper limb spasticity include pain in extremity, muscular weakness, fatigue, nausea, and bronchitis.

Adult Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® for lower limb spasticity include arthralgia, back pain, myalgia, upper respiratory tract infection, and injection-site pain.

Pediatric Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® in pediatric upper limb spasticity include upper respiratory tract infection (includes upper respiratory tract infection and viral upper respiratory tract infection), injection-site pain, nausea, constipation, rhinorrhea, nasal congestion, and seizure (includes seizure and partial seizure).

Pediatric Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX® in pediatric lower limb spasticity include injection-site erythema, injection-site pain, oropharyngeal pain, ligament sprain, skin abrasion, and decreased appetite.

Cervical Dystonia

The most frequently reported adverse reactions following injection of BOTOX® for Cervical Dystonia include dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Blepharospasm

The most frequently reported adverse reactions following injection of BOTOX® for Blepharospasm include ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Strabismus

The most frequently reported adverse events following injection of BOTOX® for Strabismus include ptosis (15.7%) and vertical deviation (16.9%).

Primary Axillary Hyperhidrosis

The most frequently reported adverse events (3%-10% of adult patients) following injection of BOTOX® for severe primary axillary hyperhidrosis in double-blind studies include injection-site pain and hemorrhage, nonaxillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

Postmarketing Experience

Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

Please see additional Important Safety Information about BOTOX® on following page.

BOTOX® Savings Program Terms and Conditions

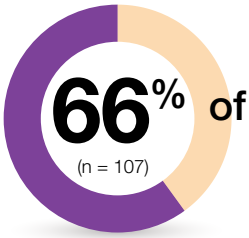
Program Terms, Conditions, and Eligibility Criteria: 1. This offer is good for use only with a valid prescription for BOTOX® (onabotulinumtoxinA). **2.** Based on insurance coverage, each patient can be reimbursed up to $1500 per treatment with a maximum savings limit of $4000 per year. Patient out-of-pocket expense may vary. **3.** This offer is not valid for use by patients enrolled in Medicare, Medicaid, or other federal or state programs (including any state pharmaceutical assistance programs), or private indemnity or HMO insurance plans that reimburse you for the entire cost of your prescription drugs. Patients may not use this offer if they are Medicare-eligible and enrolled in an employer-sponsored health plan or prescription drug benefit program for retirees. This offer is not valid for cash-paying patients. **4.** This offer is valid for 4 treatments over a 12-month period for all indications. This offer is valid for a 5th treatment for Chronic Migraine. **5.** Offer is valid only for BOTOX® and BOTOX® treatment-related costs not covered by insurance. **6.** A BOTOX® Savings Program check will be provided upon approval of a claim. The claim must be submitted with treatment details from an Explanation of Benefits (EOB) or a Specialty Pharmacy (SP) receipt. (If the BOTOX® prescription was filled by a Specialty Pharmacy, both EOB and SP details must be provided.) All claims must be submitted within 180 days of treatment date. You may be required to provide a copy of your EOB or SP receipt for your claim to be approved. **7.** A BOTOX® Savings Program check may be sent either directly to you or to your selected healthcare provider who provided treatment. For payment to be made directly to your healthcare provider, you must authorize an assignment of benefit during each claim submission. You are not obligated to assign your BOTOX® Savings Program benefit to your healthcare provider to participate in the program. **8.** Allergan® reserves the right to rescind, revoke, or amend this offer without notice. **9.** Offer good only in the USA, including Puerto Rico, at participating retail locations. **10.** Void where prohibited by law, taxed, or restricted. **11.** This offer is not health insurance. **12. By participating in the BOTOX® Savings Program, you acknowledge that you are an eligible patient and that you understand and agree to comply with the terms and conditions of this offer.**

For questions about this program, please call 1-800-44-BOTOX.

BOTOX® onabotulinumtoxinA injection

BOTOX® SAVINGS PROGRAM

BOTOX® patients depend on you to tell them about the BOTOX® Savings Program



66% of patients in the BOTOX® Savings Program hear about it from their doctor or their doctor's office staff[1]

Recommend the BOTOX® Savings Program to all commercially insured BOTOX® patients

Direct them to visit BOTOXSavingsProgram.com

Provide a BOTOX® Savings Program brochure, available from your Allergan® Representative

IMPORTANT SAFETY INFORMATION (continued)

DRUG INTERACTIONS

Co-administration of BOTOX® and other agents interfering with neuromuscular transmission (eg, aminoglycosides, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX®.

For more information on BOTOX®, please see the accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

Reference: 1. Data on file, Allergan.

Allergan an AbbVie company

MBD130546-v2 06/20 006283

Introducing the

SONIMAGE HS2

All the advanced capabilities of the HS1 System plus...

- MORE OPERATING POWER (POWER UP)
- INCREASED TOUCH SCREEN SENSITIVITY
- IMPROVED ANNOTATIONS PER APPLICATION
- IMPROVED, HANDS FREE VOICE CONTROL FOR INTERVENTIONS

FASTER FROM DIAGNOSIS TO TREATMENT | KEEP MORE ADVANCED PROCEDURES IN-HOUSE | ACCURACY OF NEEDLE PLACEMENT AND INJECTATE | PATIENT RETENTION

An Even Better Way to MSK.

The **SONIMAGE® HS2** is the newest member of the ultrasound family. The HS2 System represents our most advanced image clarity and innovative functionality. Designed with the point-of-care clinician in mind, our superior image quality and combination of touch and physical controls lead to better patient outcomes, sooner.

Visit the **Konica Minolta Healthcare virtual booth at the AAPM&R Annual Meeting** to discover the new SONIMAGE HS2, complete with superior image quality that enhances signal penetration, improves resolution and increases color flow sensitivity allowing for detailed musculoskeletal tissue differentiation and detection of small structures. The HS2 System meets all of your needs for rapid and confident diagnosis and pain management interventional procedures, helping you make even better decisions, sooner.

KONICA MINOLTA

konicaminolta.com/medicalusa

ASK THE QUESTION. START THE CONVERSATION.

Gablofen®
(baclofen injection)

INDICATIONS AND USAGE

Gablofen® (baclofen injection) is a gamma-aminobutyric acid (GABA) ergic agonist indicated for use in the management of severe spasticity of cerebral or spinal origin in adult and pediatric patients age 4 years and above. Gablofen should be reserved for patients unresponsive to oral baclofen therapy, or those who experience intolerable central nervous system side effects at effective doses. Patients should first respond to a screening dose of intrathecal baclofen prior to consideration for long term infusion via an implantable pump. Spasticity due to traumatic brain injury: wait at least one year after injury before considering Gablofen therapy.

IMPORTANT RISK INFORMATION

WARNING: DO NOT DISCONTINUE ABRUPTLY

See full prescribing information for complete boxed warning

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 rhabdomyolysis, 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 post-implant clinician and patient information.

Risk of life-threatening overdose during pump refills. Use extreme caution when filling the Medtronic SynchroMed® II Programmable Pump which is equipped with an injection port that allows direct access to the intrathecal catheter. Direct injection into the catheter through the catheter access port may cause a life-threatening overdose.

Potential for Contamination due to Non-sterile External Surface of Prefilled Syringe.

- Use only with Medtronic SynchroMed® II Programmable Pump (or other pumps labeled for intrathecal administration of Gablofen (baclofen injection)).
- Resuscitative equipment and trained staff must be available during screening dose, dose titration, and refills due to the potential life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure.

Piramal Critical Care

Full PI available at booth.

CHANGING THE COURSE OF CHRONIC PAIN MANAGEMENT STARTS WITH YOU

MITIGO™ Ⓒ II
(Morphine Sulfate Injection USP)

INJECTION DOSAGE STRENGTHS

10 mg/mL (200 mg/20mL)[2]

25 mg/mL (500 mg/20mL)[2]

INDICATIONS AND USAGE

MITIGO (Morphine Sulfate Injection, USP – Preservative-free) is an opioid agonist, for use in continuous microinfusion devices and indicated only for intrathecal or epidural infusion in the management of intractable chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

IMPORTANT RISK INFORMATION

WARNING: RISKS WITH NEURAXIAL ADMINISTRATION; LIFE-THREATENING RESPIRATORY DEPRESSION; RISK OF ADDICTION, ABUSE, AND MISUSE; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

See full prescribing information for complete boxed warning.

Single-dose neuraxial administration may result in acute or delayed respiratory depression up to 24 hours. Because of the risk of severe adverse reactions when MITIGO is administered by the epidural or intrathecal route of administration, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose.

Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Patients must be observed in a fully equipped and staffed environment for at least 24 hours after each test dose and, as indicated, for the first several days after surgery.

MITIGO exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess patient's risk before prescribing and monitor regularly for these behaviors and conditions.

Prolonged use of MITIGO during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If prolonged opioid use is required in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

WARNINGS AND PRECAUTIONS: RISKS WITH NEURAXIAL ADMINISTRATION

Control of pain by neuraxial opiate delivery, using a continuous microinfusion device, is always accompanied by considerable risk to the patients and requires a high level of skill to be successfully accomplished. The task of treating these patients must be undertaken by experienced clinical teams, well-versed in patient selection, evolving technology and emerging standards of care.

MITIGO should be administered by or under the direction of a physician experienced in the techniques of epidural or intrathecal administration and familiar with the patient management problems associated with epidural or intrathecal drug administration. The physician should be familiar with patient conditions (such as infection at the injection site, bleeding diathesis, anticoagulant therapy, etc.) which call for special evaluation of the benefit versus risk potential. Because of the risk of severe adverse effects when the epidural or intrathecal route of administration is employed, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial dose.

The facility must be equipped to resuscitate patients with severe opioid overdosage, and the personnel must be familiar with the use and limitations of specific narcotic antagonists (naloxone, naltrexone) in such cases.

For safety reasons, it is recommended that administration of MITIGO 200 mg/20 mL and 500 mg/20 mL (10 and 25 mg/mL, respectively) by the intrathecal route be limited to the lumbar area.

Piramal Critical Care

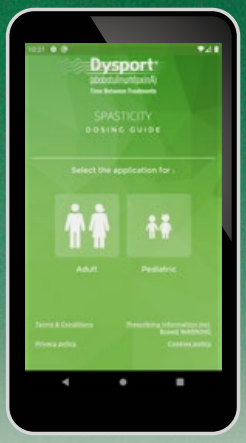
Full PI available at booth.

DYSPORT® DOSING CALCULATOR - 5 STEPS FOR TREATMENT WITH DYSPORT (abobotulinumtoxinA)

Google play

Download on the App Store

Password is Dysport



DECIDE
on the muscles based on the postures that require treatment with Dysport

DETERMINE
the amount of Dysport units to use

DILUTE
Dysport using a simplified approach

STEP 1
Determine clinical posture

STEP 2
Muscle selection

STEP 3
Decide dose selection

STEP 4
Decide dose dilution

STEP 5
Syringe preparation

INDICATIONS

Dysport® (abobotulinumtoxinA) for injection is indicated for the treatment of:

- Spasticity in patients 2 years of age and older
- Cervical dystonia in adults

IMPORTANT SAFETY INFORMATION

Warning: Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of Dysport and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses and in approved indications, cases of spread of effect have been reported at doses comparable to or lower than the maximum recommended total dose.

Contraindications

Dysport is contraindicated in patients with known hypersensitivity to any botulinum toxin products, cow's milk protein, components in the formulation or infection at the injection site(s). Serious hypersensitivity reactions including anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea have been reported. If such a reaction occurs, discontinue Dysport and institute appropriate medical therapy immediately.

Warnings and Precautions

Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of Dysport are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products, and, therefore, units of biological activity of Dysport cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method.

Dysphagia and Breathing Difficulties

Treatment with Dysport and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant side effects occur, additional respiratory muscles may be involved. Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised. Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin.

Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of Dysport.

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

Intradermal Immune Reaction

The possibility of an immune reaction when injected intradermally is unknown. The safety of Dysport for the treatment of hyperhidrosis has not been established. Dysport is approved only for intramuscular injection.

Most Common Adverse Reactions

Adults with lower limb spasticity (≥5%): falls, muscular weakness, and pain in extremity and with **upper limb spasticity** (≥4%): muscular weakness.

Pediatric patients with lower limb spasticity (≥10%): nasopharyngitis, cough and pyrexia and with **upper limb spasticity** (≥10%): upper respiratory tract infection and pharyngitis.

Adults with cervical dystonia (≥5%): muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, musculoskeletal pain, dysphonia, injection site pain, and eye disorders.

Drug Interactions

Co-administration of Dysport and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of botulinum toxin may be potentiated. Use of anticholinergic drugs after administration of Dysport may potentiate systemic anticholinergic effects, such as blurred vision. The effect of administering different botulinum neurotoxins at the same time or within several months of each other is unknown. Excessive weakness may be exacerbated by another administration of botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of Dysport.

Special Populations

Use in Pregnancy

There are no adequate and well-controlled studies in pregnant women. Dysport should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on animal data, Dysport may cause fetal harm.

Pediatric Use

The safety and effectiveness of Dysport injected into proximal muscles of the lower limb for the treatment of spasticity in pediatric patients has not been established. Based on animal data Dysport may cause atrophy of injected and adjacent muscles; decreased bone growth, length, and mineral content; delayed sexual maturation; and decreased fertility.

Geriatric Use

In general, elderly patients should be observed to evaluate their tolerability of Dysport, due to the greater frequency of concomitant disease and other drug therapy. Subjects aged 65 years and over who were treated with Dysport for lower limb spasticity reported a greater percentage of fall and asthenia as compared to those younger (10% vs. 6% and 4% vs. 2%, respectively).

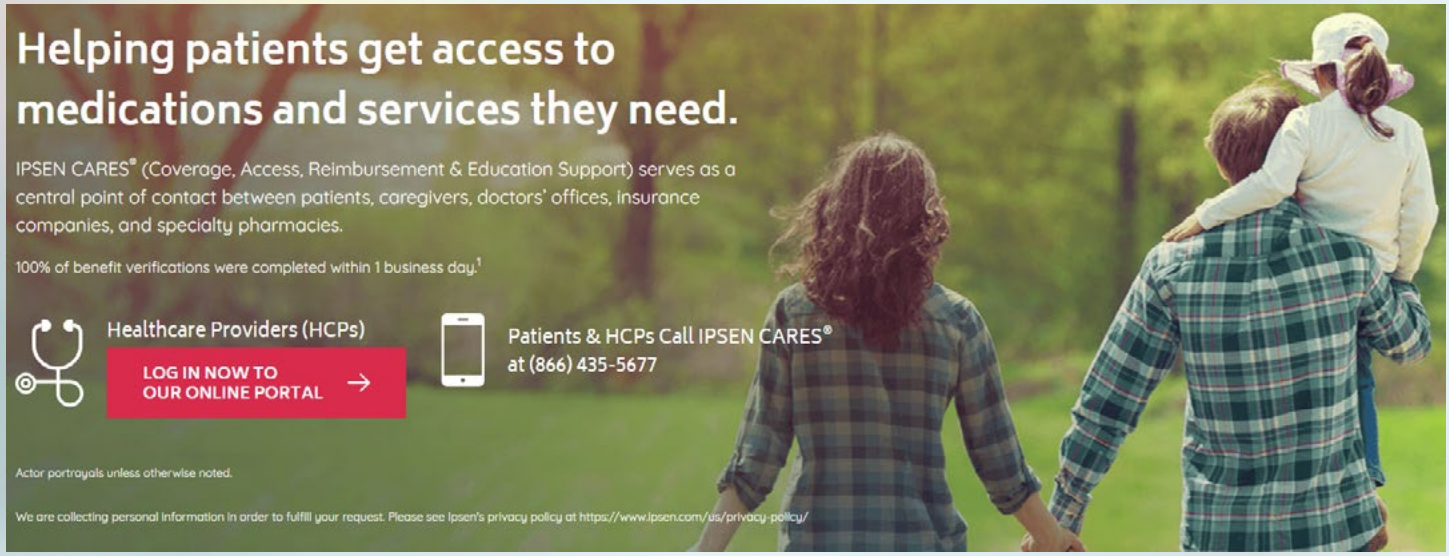
To report SUSPECTED ADVERSE REACTIONS or product complaints, contact Ipsen at 1-855-463-5127. You may also report SUSPECTED ADVERSE REACTIONS to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information, including Boxed Warning and Medication Guide.

IPSEN
Innovation for patient care

Dysport® (abobotulinumtoxinA) *It's Time*

What IPSEN CARES® Offers



IPSEN CARES provides information for you and your eligible patients to help with patient access to medication

- Benefit Verification
- Prior Authorization Information
- Appeals Information
- Patient Assistance Program
- Referrals to Specialty Pharmacy Network
- Provider Portal Technical Help

Please see Full Prescribing Information, including **Boxed Warning**, available at this presentation.

Dysport®
(abobotulinumtoxinA)

PROMETRA® II

For the Relief of Spasticity

NOT ALL PUMPS ARE THE SAME

CONSISTENTLY ACCURATE

The Prometra II pump is consistently accurate to within 3% of your prescription, which means the amount of medication treating your spasticity will be the same from when the pump is full to when it's almost empty.

LONGER BATTERY LIFE

The Prometra II pump has a 10-year battery life, which means less replacement surgeries for you compared to other pumps on the market.

SAFE, RELIABLE PERFORMANCE

The Prometra II pump design provides safeguards to help your clinical team confidently refill your pump, and its motor-less design eliminates the concerns that other pumps have with stalling.

LIVE YOUR LIFE with FEWER RESTRICTIONS

The Prometra II pump is less affected by environmental conditions like altitude and temperature, which means you can have confidence at all times when performing activities of daily living.

FLOWONIX

Visit **flowonix.com**
for more information and ask your doctor today
if Prometra II can help **redefine your potential**.

Brief Statement for US Consumers | PL-19701-02 | Issue date: November 2019

IMPORTANT SAFETY INFORMATION FOR PROMETRA DRUG DELIVERY SYSTEMS - BRIEF STATEMENT. **Indications:** The Prometra® Programmable Infusion Pump System is indicated for intrathecal infusion of drug therapy, including: Infumorph® (preservative free morphine sulfate sterile solution), preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP), and baclofen (baclofen injection, intrathecal, 500-2000 mcg/mL). The pump is indicated for use in adult populations of 22 years and older. **Drug Information:** See drug labeling for indications, contraindications, warnings, precautions, adverse reactions and under/over dose symptoms. Tell your doctor about any drug related signs or symptoms you may experience. **Contraindications**: The Prometra pump system should not be implanted if: you have an infection; your body type cannot safely accommodate the pump size and weight; the pump cannot be implanted 1 inch below the skin; you have allergies to catheter or pump materials; you have had an intolerance to implanted devices in the past; your spinal column anatomy obstructs cerebrospinal fluid flow or prevents intrathecal drug delivery; you are deemed an unsuitable candidate after psychological evaluation; you have an occupation with exposure to high current industrial equipment, powerful magnets or transmitting towers; you require hyperbaric therapy. **Warnings**: FAILURE TO EMPTY THE PUMP PRIOR TO EXPOSURE TO MRI ENVIRONMENT COULD RESULT IN DRUG OVERDOSE THAT COULD LEAD TO SERIOUS PATIENT INJURY OR DEATH; USE OF UNAPPROVED DRUGS (e.g., DRUG COCKTAILS, PHARMACY COMPOUNDED DRUGS, MORPHINE WITH PRESERVATIVES, ETC.) WITH THE PROMETRA II PUMP COULD RESULT IN PUMP FAILURE AND/OR SERIOUS ADVERSE EVENTS SUCH AS SEVERE UNDERDOSE, OVERDOSE OR DEATH. If an MRI is required, your doctor MUST empty your pump of all medication prior to the MRI. **Precautions:** Tell your doctor about any new neurological signs or overdose/withdrawal symptoms you may experience. Pain on injection may be early sign of infection. Seek immediate medical attention if you experience early signs of baclofen under-dose or withdrawal. **Adverse Events:** Pocket seroma/hematoma with or without infection, pump site skin erosion, pump rotation/migration/flipping or twisting, adverse reaction to pump materials, granuloma; infection in intrathecal space, including meningitis, nerve damage. Additional potential adverse events are included in the Patient Guide. For full disclosure of contraindications, warnings, precautions, adverse events and MRI Instructions, please call Flowonix at 855-356-9665 and/or consult Flowonix website at Flowonix.com. **Caution**: Federal Law (USA) restricts this device to sale by or on the order of a physician. FLOWONIX and PROMETRA are trademarks of Flowonix Medical, Inc.

PL-15600-00 February 2020

FLOWONIX
flowonix.com

Clinically established and trusted for over 25 years in the management of severe spasticity

- Extensive clinical data with established safety and efficacy profiles
- Lioresal® Intrathecal (baclofen injection) is the only intrathecal baclofen to undergo dynamic drug testing in catheters representative of the entire Medtronic SynchroMed™ II Drug Infusion System portfolio [1,2]
- Suitable for use in aseptic environments, such as operating rooms
- Strict conformance to labeled concentrations (+/– 5% of listed concentration) to ensure consistent results and patient safety [1]

- Refill kit included
- Free overnight shipping on all orders

Ampule presentation to ensure quality of medication

- Minimize drug contact with constituents
- Minimize risk from leachables and extractables

Saol Customer Service

1.877.594.9546

For more information, including **BOXED WARNING**, refer to Lioresal® Intrathecal (baclofen injection) prescribing information, attached to this brochure.

1. Lioresal New Drug Application
2. Data on file

Lioresal®
Intrathecal (baclofen injection)

Lioresal® Intrathecal (baclofen injection)

Important Safety Information

Indications and Usage

- Lioresal® Intrathecal (baclofen injection) is a muscle relaxant and antispastic that is indicated for use in the management of severe spasticity of cerebral or spinal origin.
- Lioresal® Intrathecal 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® Intrathecal into the intrathecal space.
- For patients with spasticity of spinal origin, Lioresal® Intrathecal 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.
- Prior to implantation of a device for chronic intrathecal infusion of Lioresal® Intrathecal, patients must show a response to Lioresal® Intrathecal in a screening trial. Please review the dosing and administration section of the Lioresal® Intrathecal prescribing information for further details.

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 rhabdomyolysis, 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 postimplant clinician and patient information (see WARNINGS).

Contraindications

- Hypersensitivity to baclofen
- Lioresal® Intrathecal is not recommended for intravenous, intramuscular, subcutaneous or epidural administration.

Select Warnings and Precautions

- It is mandatory that all patients, caregivers, and treating physicians receive adequate information regarding the risks of the mode of treatment. Instruction should be given on signs and symptoms of overdose, procedures to be followed in the event of an overdose, and proper home care of the pump and insertion site.
- Due to the possibility of life-threatening CNS depression, cardiovascular collapse, and/or respiratory failure, physicians must be adequately trained and educated in chronic intrathecal infusion therapy.
- Patients should be infection-free prior to both a screening trial and a pump implantation. The presence of infection may interfere with an assessment of the patient's response to bolus Lioresal® Intrathecal (baclofen injection), increase the risk of surgical complications and complicate dosing.
- Reservoir refilling must be performed by fully trained and qualified personnel following the directions provided by the pump manufacturer. Extreme caution must be used when filling an FDA approved implantable pump, following strict aseptic technique and ensuring refill directly into the reservoir and not the catheter access port.
- An attempt should be made to discontinue concomitant oral antispasticity medication to avoid possible overdose or adverse drug interactions, either prior to screening or following implant and initiation of chronic Lioresal® Intrathecal infusion.
- Following pump implantation, and for each adjustment of the dosing rate of the pump and/or concentration of Lioresal® Intrathecal, the patient should be monitored closely until it is certain the patient's response to the infusion is acceptable and reasonably stable.
- Early symptoms of baclofen withdrawal may include return of baseline spasticity, pruritus, hypotension and paresthesias.
- Priapism may develop or recur if treatment with intrathecal baclofen is interrupted.
- Signs of overdose may appear suddenly or insidiously, and a massive overdose may present as coma. Less sudden and/or less severe forms of overdose may present with signs of drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia 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 pump reservoir.
- Delivery of more drug volume than the programmed rate (overinfusion) can result in unexpected overdose, or withdrawal caused by early emptying of the pump reservoir. Refer to the manufacturer's pump manual and instructions for refilling the reservoir.
- Except in overdose related emergencies, the dose of Lioresal® Intrathecal should ordinarily be reduced slowly if the drug is discontinued for any reason.

Adverse Reactions

Common Adverse Reactions

- The most frequent drug adverse events 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%). Dosing and programming errors may result in clinically significant overdose or withdrawal. Acute massive overdose may result in coma and may be life threatening.
- Drowsiness has been reported in patients on Lioresal® Intrathecal. 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 Lioresal® Intrathecal may be additive to those of alcohol and other CNS depressants.

Serious Adverse Reactions

- Seizures have been reported during overdose and with withdrawal from Lioresal® Intrathecal (baclofen injection) as well as in patients maintained on therapeutic doses of Lioresal® Intrathecal.
- Fatalities have been reported with Lioresal® Intrathecal use.

Postmarketing Experience

- The following adverse events have been reported during post-approval use of Lioresal® Intrathecal.
  - Musculoskeletal – The onset of scoliosis or worsening of a pre-existing scoliosis has been reported.
  - Urogenital – Sexual dysfunction in men and women including decreased libido and orgasm dysfunction have been reported.

Use in Specific Populations

- There are no adequate and well controlled studies in pregnant women. Lioresal® Intrathecal should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
- Nursing mothers should exercise caution, as oral baclofen has been shown to pass into milk at therapeutic doses.
- Safety and effectiveness in pediatric patients below the age of 4 have not been established.
- Patients suffering from psychotic disorders, schizophrenia, or confusional states should be treated cautiously with Lioresal® Intrathecal and kept under careful surveillance.
- Lioresal® Intrathecal should be given with caution in patients with impaired renal function. Dose reduction may be necessary.
- Lioresal® Intrathecal should be used with caution in patients with a history of autonomic dysreflexia.

For more information, including **BOXED WARNING**, refer to Lioresal® Intrathecal (baclofen injection) prescribing information, attached to this brochure.

SAOL™ THERAPEUTICS

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Rev. 03/2020

ST-111-1070-02

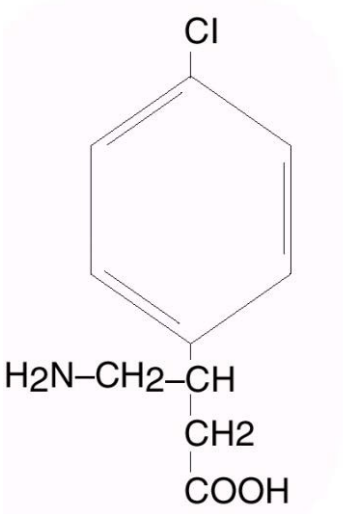
LIORESAL® INTRATHECAL
(baclofen injection)

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 rhabdomyolysis, 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 postimplant clinician and patient information (see WARNINGS).

DESCRIPTION

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



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 INTRATHECAL 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 INTRATHECAL contains baclofen U. S. P. 50 mcg, 500 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 any 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 $GABA_B$ receptor subtype.

LIORESAL INTRATHECAL 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 INTRATHECAL:

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 response, and duration of action may vary with individual patients depending on 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 INTRATHECAL'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 INTRATHECAL:

The pharmacokinetics of CSF clearance of LIORESAL INTRATHECAL calculated from intrathecal bolus or continuous infusion studies approximates CSF turnover, suggesting elimination is by bulk-flow removal of CSF.

Intrathecal Bolus: After a bolus lumbar injection of 50 or 100 mcg LIORESAL INTRATHECAL 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 30 mL/hour.

Continuous Infusion: The mean CSF clearance for LIORESAL INTRATHECAL (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 (0-5 ng/mL).

Limited pharmacokinetic data suggest that a lumbar-cisternal concentration gradient of about 4:1 is established along the neuroaxis during baclofen infusion. This is based upon simultaneous CSF sampling via cisternal 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 AND USAGE

LIORESAL INTRATHECAL (baclofen injection) 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 INTRATHECAL 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 INTRATHECAL 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 INTRATHECAL into the intrathecal space.

Spasticity of Spinal Cord Origin: Evidence supporting the efficacy of LIORESAL INTRATHECAL was obtained in randomized, 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 randomized controlled cross-over trial of 51 patients with cerebral palsy, provided strong, statistically significant results; LIORESAL INTRATHECAL 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= 0.066) and provided directionally favorable results. The last study, however, did not provide data that could be reliably analyzed.

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

CONTRAINDICATIONS

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

WARNINGS

LIORESAL INTRATHECAL 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 INTRATHECAL injection is adequately evaluated. Evaluation (consisting of a screening procedure: see Dosage and Administration) requires that LIORESAL INTRATHECAL 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 section.

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.

On each occasion that the dosing rate of the pump and/or the concentration of LIORESAL INTRATHECAL (baclofen injection) in the reservoir is adjusted, close medical monitoring is required until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

It is mandatory that the patient, all patient caregivers, and the physicians 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 overdose may appear suddenly or insidiously. Acute massive overdose may present as coma. Less sudden and/or less severe forms of overdose may present with signs of drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia 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, inadvertent subcutaneous injection, 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 refilled through the reservoir refill septum. Inadvertent injection into the subcutaneous tissue can occur if the reservoir refill septum is not properly accessed. 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 or inadvertent injection into the subcutaneous tissue 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 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. 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. Cases of intrathecal mass at the tip of the implanted catheter leading to withdrawal symptoms have also been reported, most of them involving pharmacy compounded analgesic admixtures (see PRECAUTIONS).

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. Early symptoms of baclofen withdrawal may include return of baseline spasticity, pruritus, hypotension, and paresthesias. Priapism may develop or recur if treatment with intrathecal baclofen is interrupted. 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.

Fatalities:

Spasticity of Spinal Cord Origin: There were 16 deaths reported among the 576 U.S. patients treated with LIORESAL INTRATHECAL (baclofen injection) in pre- and post- marketing studies evaluated as of December 1992. Because these patients were treated under uncontrolled clinical settings, it is impossible to determine definitively what role, if any, LIORESAL INTRATHECAL played in their deaths.

As a group, the patients who died were relatively young (mean age was 47 with a range from 25 to 63), but the majority suffered from severe spasticity of many years duration, were nonambulatory, had various medical complications such as pneumonia, urinary tract infections, and decubiti, and/or had received multiple concomitant medications. A case-by-case review of the clinical course of the 16 patients who died failed to reveal any unique signs, symptoms, or laboratory results that would suggest that treatment with LIORESAL INTRATHECAL caused their deaths. Two patients, however, did suffer sudden and unexpected death within 2 weeks of pump implantation and one patient died unexpectedly after screening.

One patient, a 44 year old male with MS, died in hospital on the second day following pump implantation. An autopsy demonstrated severe fibrosis of the coronary conduction system. A second patient, a 52 year old woman with MS and a history of an inferior wall myocardial infarction, was found dead in bed 12 days after pump implantation, 2 hours after having had documented normal vital signs. An autopsy revealed pulmonary congestion and bilateral pleural effusions. It is impossible to determine whether LIORESAL INTRATHECAL contributed to these deaths. The third patient underwent three baclofen screening trials. His medical history included SCI, aspiration pneumonia, septic shock, disseminated intravascular coagulopathy, severe metabolic acidosis, hepatic toxicity, and status epilepticus. Twelve days after screening (he was not implanted), he again experienced status epilepticus with subsequent significant neurological deterioration. Based upon prior instruction, extraordinary resuscitative measures were not pursued and the patient died.

Spasticity of Cerebral Origin: There were three deaths occurring among the 211 patients treated with LIORESAL INTRATHECAL in pre- marketing studies as of March 1996. These deaths were not attributed to the therapy.

Overinfusion –Delivery of more drug volume than the programmed rate (overinfusion) can result in unexpected overdose, or withdrawal caused by early emptying of the pump reservoir. Refer to the

manufacturer's pump manual and instructions for refilling the reservoir.

PRECAUTIONS

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.

Screening

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

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 fully trained and qualified personnel following the directions provided by the pump manufacturer. Inadvertent injection into the subcutaneous tissue can occur if the reservoir refill septum is not properly accessed. Subcutaneous injection may result in symptoms of a systemic overdose or early depletion of the reservoir. Refill intervals should be carefully calculated to prevent depletion of the reservoir, as this would result in the return of severe spasticity and possibly symptoms of withdrawal.

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 catheter 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 support circulatory function, 2) possibly 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 LIORESAL INTRATHECAL should ordinarily be reduced slowly if the drug is discontinued for any reason.

An attempt should be made to discontinue concomitant oral antispasticity medication to avoid possible overdose or adverse drug interactions, either prior to screening or following implant and initiation of chronic LIORESAL INTRATHECAL infusion. Reduction and discontinuation of oral anti-spasmotics should be done slowly and with careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispastics should be avoided.

Drowsiness: Drowsiness has been reported in patients on LIORESAL INTRATHECAL. 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 LIORESAL INTRATHECAL (baclofen injection) may be additive to those of alcohol and other CNS depressants.

Intrathecal mass: Cases of intrathecal mass at the tip of the implanted catheter have been reported, most of them involving pharmacy compounded analgesic admixtures. The most frequent symptoms associated with intrathecal 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. In patients with new neurological signs or symptoms suggestive of an intrathecal 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 intrathecal mass.

Precautions in special patient populations: Careful dose titration of LIORESAL INTRATHECAL 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 psychotic disorders, schizophrenia, or confusional states should be treated cautiously with LIORESAL INTRATHECAL and kept under careful surveillance, because exacerbations of these conditions have been observed with oral administration.

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

Because LIORESAL 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 LIORESAL INTRATHECAL.

DRUG INTERACTIONS

There is inadequate systematic experience with the use of LIORESAL INTRATHECAL in combination with other medications to predict specific drug-drug interactions. Interactions attributed to the combined use of LIORESAL INTRATHECAL and epidural morphine include hypotension and dyspnea. *CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY*

No increase in tumors was seen in rats receiving baclofen orally for two years. Adequate genotoxicity assays of baclofen have not been performed.

PREGNANCY

There are no adequate and well-controlled studies in pregnant women. In animal studies, baclofen had adverse effects on embryofetal development when administered orally to pregnant rats. LIORESAL INTRATHECAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Baclofen given orally increased the incidence of fetal structural abnormalities (omphaloceles) in rats. Reductions in food intake and body weight gain were observed in the dams. Fetal structural abnormalities were not observed in mice or rabbits

NURSING MOTHERS

In mothers treated with oral LIORESAL (baclofen USP) in therapeutic doses, the active substance passes into the milk. It is not known whether detectable levels of drug are present in milk of nursing mothers receiving LIORESAL INTRATHECAL. As a general rule, nursing should be undertaken while a patient is receiving LIORESAL INTRATHECAL 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.

Considerations based on experience with oral LIORESAL (baclofen USP)

A dose-related increase in incidence of ovarian cysts was observed in female rats treated chronically with oral LIORESAL. Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients who were treated with oral LIORESAL 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 REACTIONS

Spasticity of Spinal Cord Origin – Clinical Studies:

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 LIORESAL INTRATHECAL (baclofen injection) which were not seen at an equivalent incidence among placebo-treated patients were: somnolence, dizziness, nausea, hypotension, headache, convulsions and hypotonia.

Associated with Discontinuation of Treatment — 8/474 patients with spasticity of spinal cord origin receiving long term infusion of LIORESAL INTRATHECAL 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), gynecological fibroids (1) and pump overpressurization (1) with unknown, if any, sequela. Eleven patients who developed coma secondary to overdose had their treatment temporarily suspended, but all were subsequently restarted and were not, therefore, considered to be true discontinuations.

Fatalities — See Warnings.

Incidence in Controlled Trials — Experience with LIORESAL 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 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 LIORESAL INTRATHECAL (baclofen injection) in two randomized, placebo-controlled trials: hypotension (2), dizziness (2), headache (2), dyspnea (1). No adverse events were reported among the 32 patients receiving placebo in these studies.

Events Observed during the Pre- and Post-marketing Evaluation of LIORESAL INTRATHECAL — Adverse events associated with the use of LIORESAL INTRATHECAL reflect experience gained with 576 patients followed prospectively in the United States. They received LIORESAL INTRATHECAL for periods of one day (screening) (N = 576) to over eight years (maintenance) (N = 10). The usual screening bolus dose administered prior to pump implantation in these studies was typically 50 mcg. The maintenance dose ranged from 12 mcg to 2003 mcg per day. Because of the open, uncontrolled nature of the experience, a causal linkage between events observed and the administration of LIORESAL INTRATHECAL 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 more commonly reported reactions— hypotonia, somnolence, dizziness, paresthesia, nausea/vomiting and headache— appear clearly drug-related.

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 a discontinuation of long term treatment in the pre- and post-marketing studies.

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

	Percent of Patients Reporting Events		
	N = 576	**N = 474**	**N = 430**
	Screening[a]	Titration[b]	Maintenance[c]
Adverse Event	**Percent**	**Percent**	**Percent**
Hypotonia	5.4	13.5	25.3
Somnolence	5.7	5.9	20.9
Dizziness	1.7	1.9	7.9
Paresthesia	2.4	2.1	6.7
Nausea and Vomiting	1.6	2.3	5.6
Headache	1.6	2.5	5.1
Constipation	0.2	1.5	5.1
Convulsion	0.5	1.3	4.7
Urinary Retention	0.7	1.7	1.9
Dry Mouth	0.2	0.4	3.3
Accidental Injury	0.0	0.2	3.5
Asthenia	0.7	1.3	1.4
Confusion	0.5	0.6	2.3
Death	0.2	0.4	3.0
Pain	0.0	0.6	3.0
Speech Disorder	0.0	0.2	3.5
Hypotension	1.0	0.2	1.9
Ambylopia	0.5	0.2	2.3
Diarrhea	0.0	0.8	2.3
Hypoventilation	0.2	0.8	2.1
Coma	0.0	1.5	0.9
Impotence	0.2	0.4	1.6
Peripheral Edema	0.0	0.0	2.3
Urinary Incontinence	0.0	0.8	1.4
Insomnia	0.0	0.4	1.6
Anxiety	0.2	0.4	0.9
Depression	0.0	0.0	1.6
Dyspnea	0.3	0.0	1.2
Fever	0.5	0.2	0.7
Pneumonia	0.2	0.2	1.2
Urinary Frequency	0.0	0.6	0.9
Urticaria	0.2	0.2	1.2
Anorexia	0.0	0.4	0.9
Diplopia	0.0	0.4	0.9
Dysautonomia	0.2	0.2	0.9
Hallucinations	0.3	0.4	0.5
Hypertension	0.2	0.6	0.5

[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
%=% 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 LIORESAL INTRATHECAL (baclofen injection) from foreign studies has been reported. The

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

	Percent of Patients Reporting Events		
	N = 576	**N = 474**	**N = 430**
	Screening[a]	Titration[b]	Maintenance[c]
Adverse Event	**Percent**	**Percent**	**Percent**
Hypotonia	5.4	13.5	25.3
Somnolence	5.7	5.9	20.9
Dizziness	1.7	1.9	7.9
Paresthesia	2.4	2.1	6.7
Nausea and Vomiting	1.6	2.3	5.6
Headache	1.6	2.5	5.1
Constipation	0.2	1.5	5.1
Convulsion	0.5	1.3	4.7
Urinary Retention	0.7	1.7	1.9
Dry Mouth	0.2	0.4	3.3
Accidental Injury	0.0	0.2	3.5
Asthenia	0.7	1.3	1.4
Confusion	0.5	0.6	2.3
Death	0.2	0.4	3.0
Pain	0.0	0.6	3.0
Speech Disorder	0.0	0.2	3.5
Hypotension	1.0	0.2	1.9
Ambylopia	0.5	0.2	2.3
Diarrhea	0.0	0.8	2.3
Hypoventilation	0.2	0.8	2.1
Coma	0.0	1.5	0.9
Impotence	0.2	0.4	1.6
Peripheral Edema	0.0	0.0	2.3
Urinary Incontinence	0.0	0.8	1.4
Insomnia	0.0	0.4	1.6
Anxiety	0.2	0.4	0.9
Depression	0.0	0.0	1.6
Dyspnea	0.3	0.0	1.2
Fever	0.5	0.2	0.7
Pneumonia	0.2	0.2	1.2
Urinary Frequency	0.0	0.6	0.9
Urticaria	0.2	0.2	1.2
Anorexia	0.0	0.4	0.9
Diplopia	0.0	0.4	0.9
Dysautonomia	0.2	0.2	0.9
Hallucinations	0.3	0.4	0.5
Hypertension	0.2	0.6	0.5

[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
%=% 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 LIORESAL 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, vasodilitation, cerebrovascular accident, nystagmus, personality disorder, psychotic depression, cerebral ischemia, emotional lability, euphoria, hypertonia, ileus, drug dependence, incoordination, paranoid reaction and ptosis.

Digestive System: Flatulence, dysphagia, dyspepsia and gastroenteritis.

Cardiovascular: Postural hypotension, bradycardia, palpitations, syncope, arrhythmia ventricular, deep thrombophlebitis, pallor and tachycardia.

Respiratory: Respiratory disorder, aspiration pneumonia, hyperventilation, pulmonary embolus and rhinitis.

Urogenital: Hematuria and kidney failure.

Skin and Appendages: Alopecia and sweating.

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

Special Senses: 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 – Clinical Studies:

Commonly Observed — In pre-marketing clinical trials, the most commonly observed adverse events associated with use of LIORESAL 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 LIORESAL 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 LIORESAL 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 LIORESAL 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 LIORESAL 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 LIORESAL INTRATHECAL — Adverse events associated with the use of LIORESAL 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 LIORESAL 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 LIORESAL 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.

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

	Percent of Patients Reporting Events		
	N = 211	**N = 153**	**N = 150**
	Screening[a]	Titration[b]	Maintenance[c]
Adverse Event	**Percent**	**Percent**	**Percent**
Hypotonia	2.4	14.4	34.7
Somnolence	7.6	10.5	18.7
Headache	6.6	7.8	10.7
Nausea and Vomiting	6.6	10.5	4.0
Vomiting	6.2	8.5	4.0
Urinary Retention	0.9	6.5	8.0
Convulsion	0.9	3.3	10.0
Dizziness	2.4	2.6	8.0
Nausea	1.4	3.3	7.3
Hypoventilation	1.4	1.3	4.0
Hypertonia	0.0	0.7	6.0
Paresthesia	1.9	0.7	3.3
Hypotension	1.9	0.7	2.0
Increased Salivation	0.0	2.6	2.7
Back Pain	0.9	0.7	2.0
Constipation	0.5	1.3	2.0
Pain	0.0	0.0	4.0
Pruritus	0.0	0.0	4.0
Diarrhea	0.5	0.7	2.0
Peripheral Edema	0.0	0.0	3.3
Thinking Abnormal	0.5	1.3	0.7
Agitation	0.5	0.0	1.3
Asthenia	0.0	0.0	2.0
Chills	0.5	0.0	1.3
Coma	0.5	0.0	1.3
Dry Mouth	0.5	0.0	1.3
Pneumonia	0.0	0.0	2.0
Speech Disorder	0.5	0.7	0.7
Tremor	0.5	0.0	1.3
Urinary Incontinence	0.0	0.0	2.0
Urination Impaired	0.0	0.0	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.

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:

Nervous System: Akathisia, ataxia, confusion, depression, opisthotonos, amnesia, anxiety, hallucinations, hysteria, insomnia, nystagmus, personality disorder, reflexes decreased, and vasodilitation.

Digestive System: Dysphagia, fecal incontinence, gastrointestinal hemorrhage and tongue disorder.
Cardiovascular: Bradycardia.
Respiratory: Apnea, dyspnea and hyperventilation.
Urogenital: Abnormal ejaculation, kidney calculus, oliguria and vaginitis.
Skin and Appendages: Rash, sweating, alopecia, contact dermatitis and skin ulcer.
Special Senses: Abnormality of accommodation.
Body as a Whole: Death, fever, abdominal pain, carcinoma, malaise and hypothermia.
Hemic and Lymphatic System: Leukocytosis and petechial rash.

Postmarketing Experience:

The following adverse events have been reported during post-approval use of LIORESAL INTRATHECAL. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Musculoskeletal: The onset of scoliosis or worsening of a pre-existing scoliosis has been reported.
Urogenital: Sexual dysfunction in men and women, including decreased libido and orgasm dysfunction, have been reported. Erectile dysfunction in men has also been reported. Priapism has been reported following baclofen withdrawal.

OVERDOSAGE

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 re introduction of LIORESAL INTRATHECAL after a period of interruption in therapy.

Symptoms of LIORESAL INTRATHECAL Overdose: Drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, hypothermia, seizures, rostral progression of hypotonia and loss of consciousness progressing 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 mcg 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, until the drug is eliminated.

If lumbar puncture is not contraindicated, consideration should be given to withdrawing 30-40 mL of CSF to reduce CSF baclofen concentration.

DOSAGE AND 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 mcg/mL. A 1 mL ampule (50 mcg/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 mcg. However, for very small patients, a screening dose of 25 mcg may be tried first. **Patients who do not respond to a 100 mcg 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 starting daily 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.

Pediatric Patients: 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 not a substantive clinical response to increases in the daily dose, check for proper pump function and catheter patency. 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 immediately available for use in case of life-threatening or intolerable 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).

Maintenance dosage for long term continuous infusion of LIORESAL INTRATHECAL (baclofen injection) has ranged from 12 mcg/day to 2003 mcg/ day, with most patients adequately maintained on 300 micrograms to 800 micrograms per day. There is limited experience with daily doses greater than 1000 mcg/day. Determination of the optimal LIORESAL INTRATHECAL dose requires individual titration. The lowest dose with an optimal response should be used.

Spasticity of Cerebral 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, or to titrate the dose to the desired degree of muscle tone for optimal functions. 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 5-20%, but no more than 20%, to maintain adequate symptom control. The daily dose may be reduced by 10-20% if patients experience side effects. Many 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).

Maintenance dosage for long term continuous infusion of LIORESAL INTRATHECAL (baclofen injection) has ranged from 22 mcg/ day to 1400 mcg/ day, with most patients adequately maintained on 90 micrograms to 703 micrograms per day. In clinical trials, only 3 of 150 patients required daily doses greater than 1000 mcg/ day.

Pediatric Patients: Use same dosing recommendations for patients with spasticity of cerebral origin. Pediatric patients under 12 years seemed to require a lower daily dose in clinical trials. Average daily dose for patients under 12 years was 274 mcg/ day, with a range of 24 to 1199 mcg/ day. Dosage requirement for pediatric patients over 12 years does not seem to be different from that of adult patients.

Determination of the optimal LIORESAL INTRATHECAL dose requires individual titration. The lowest dose with an optimal response should be used.

Potential need for dose adjustments in chronic use: During long term treatment, approximately 5% (28/627) of patients become refractory to increasing doses. There is not sufficient experience to make firm recommendations for tolerance treatment; however, this "tolerance" has been treated on occasion, in hospital, by a "drug holiday" consisting of the gradual reduction of LIORESAL INTRATHECAL over a 2 to 4 week period and switching to alternative methods of spasticity management. After the "drug holiday," LIORESAL INTRATHECAL may be restarted at the initial continuous infusion dose.

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 50 mcg 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, U.S.P.

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 packaged in single use ampules containing 0.05 mg/1 mL (50 mcg/mL), 10 mg/20 mL (500 mcg/mL), 10 mg/5 mL (2000 mcg/mL), or 40 mg/20 mL (2000 mcg/mL) supplied as follows:

Screening dose (Model 8563s): five ampules each containing 0.05 mg/1 mL (50 mcg/mL) (NDC 70257-562-55).

LIORESAL INTRATHECAL (baclofen injection) Refill Kits. Each refill kit includes the indicated amount of LIORESAL INTRATHECAL, a drug preparation kit, a pump refill kit with accessories that are compatible with Medtronic SynchroMed® Infusion Systems, and associated instructions.

Model 8561: one ampule containing 10 mg/20 mL (500 mcg/mL) (NDC 70257-560-01).

Model 8562: two ampules, each contains 10 mg/5 mL (2000 mcg/mL) (NDC 70257-561-02).

Model 8564: one ampule containing 40 mg/20 mL (2000 mcg/mL) (NDC 70257-563-01).

Model 8565: two ampules, each contains 10 mg/20 mL (500 mcg/mL) (NDC 70257-560-02).

Model 8566: two ampules, each contains 40 mg/20 mL (2000 mcg/mL) (NDC 70257-563-02).

Storage:

Does not require refrigeration.
Do not store above 86° F (30° C).
Do not freeze.
Do not heat sterilize.

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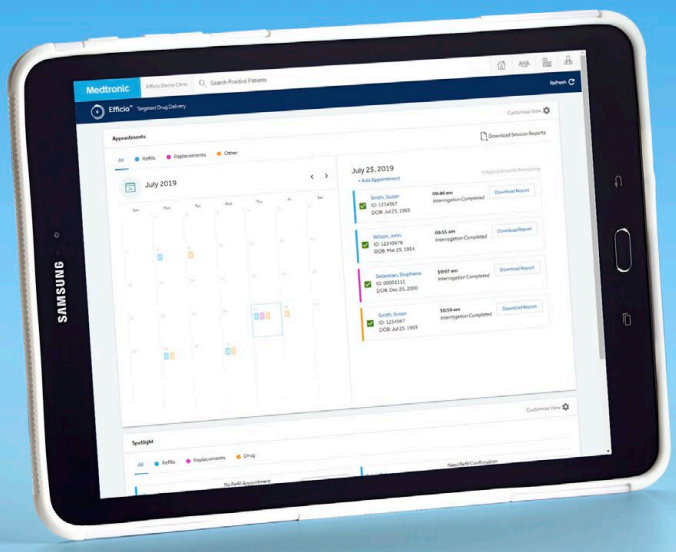

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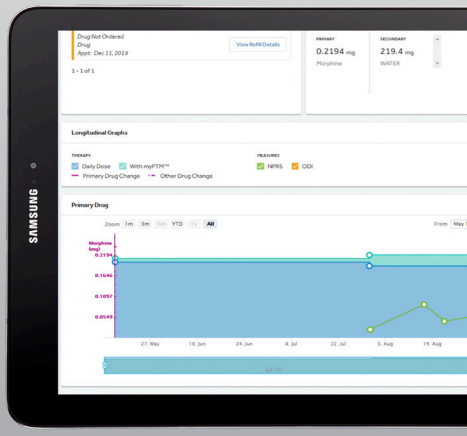
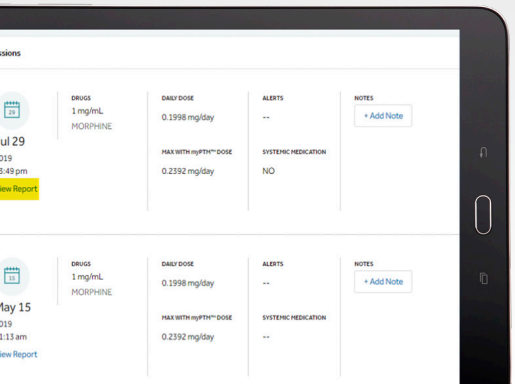


Visualized, longitudinal data helps you easily identify long-term dose trends.



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Your programming tablet will need Wi-Fi connectivity to enable data flow to Efficio™ software. Contact Medtronic Digital Connectivity at 1-800-707-0933 for assistance.

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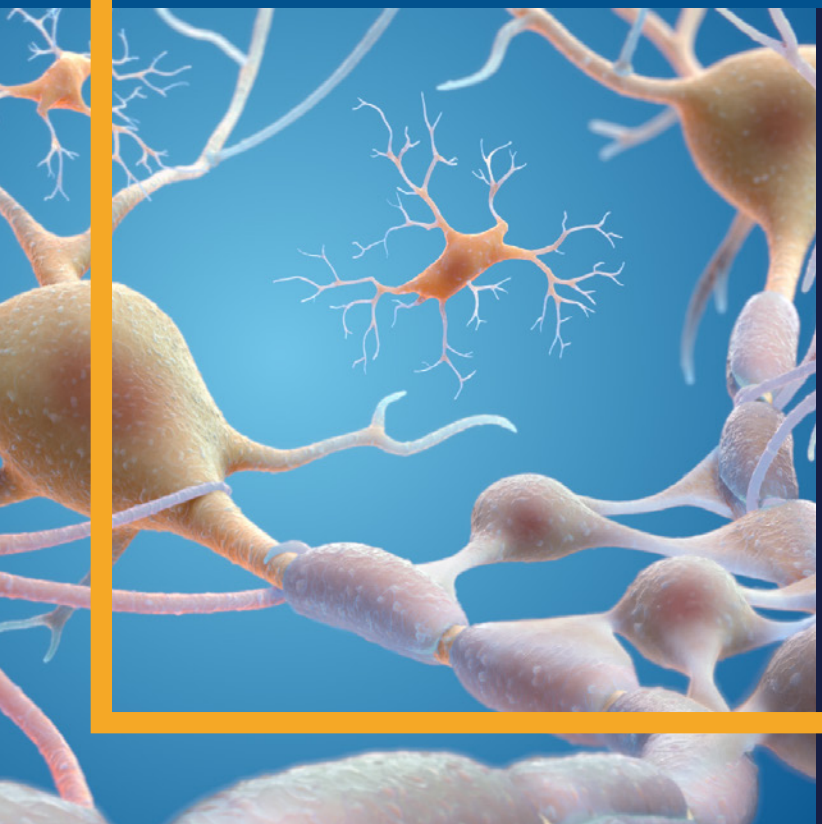
SUPERIOR PAIN RELIEF. PROVEN.

In an RCT, DTM™ SCS proved sustained superiority compared to conventional stimulation at 12 months. Proven only on the Intellis™ platform.



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BEYOND THE NEURON

Glial cells are active contributors to neural processing and various disease states, including chronic pain. In a pain state, glial cells are known to release factors that can sensitize neurons and cause pro-inflammatory responses, indicating they play a crucial role in the chronic pain process.[1-3]

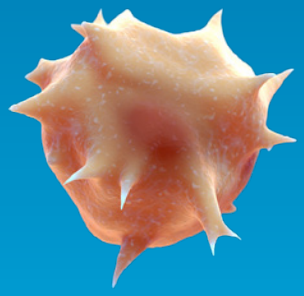
Furthermore, decades of basic science research have discovered glial cells outnumber neurons 12:1 in the spinal cord.[4] Pre-clinical evidence suggests glial cells can be modulated with electrical stimuli, resulting in the release of neurotransmitters, impacting cell-to-cell communication.[1]

BEHIND THE SCIENCE

Glial cells[2]:

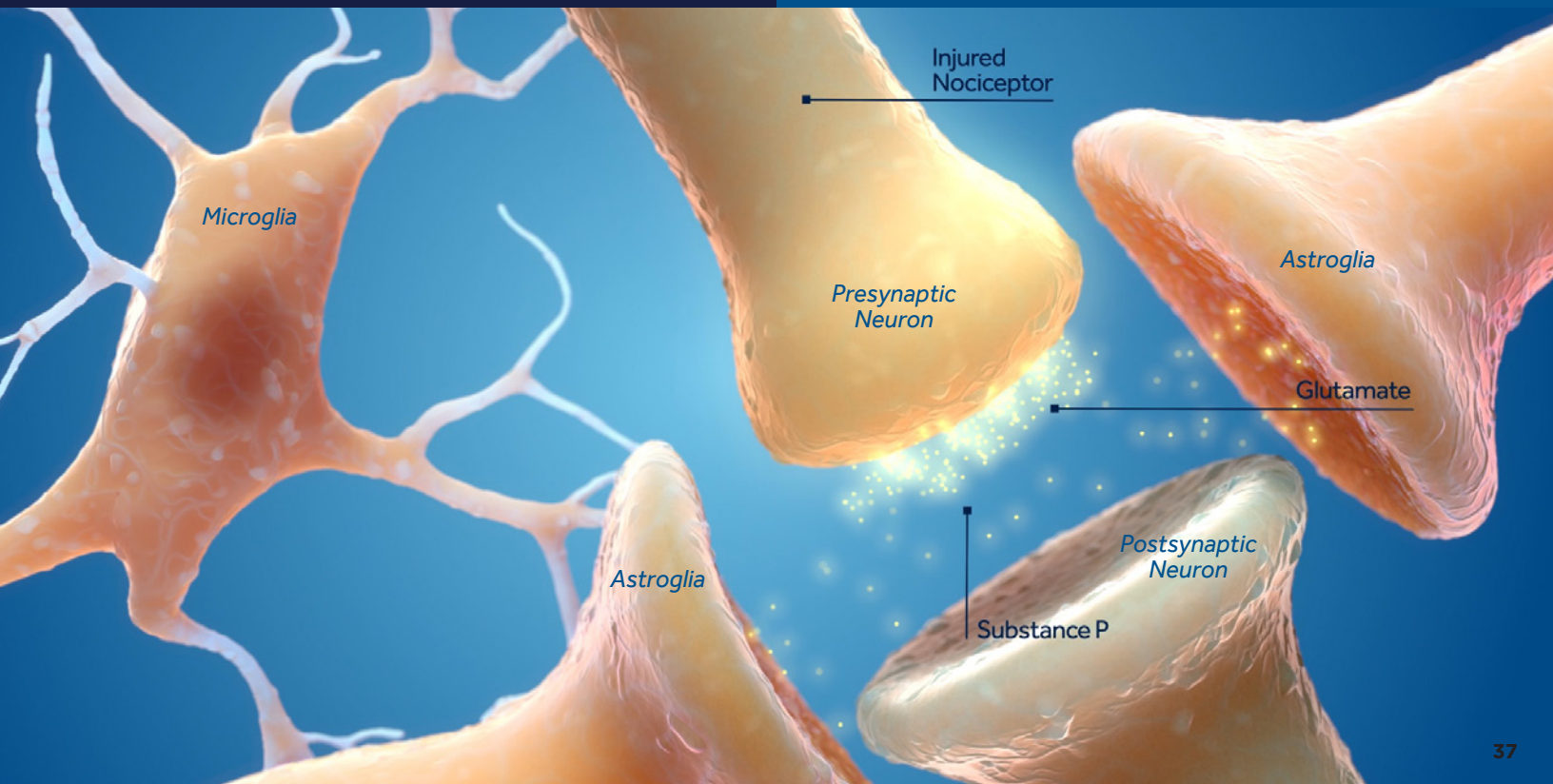
- Are key contributors to chronic pain mechanisms
- Respond to neuronal signaling molecules
- Release signaling molecules *(that can be protective or pathological)*
- Release inflammatory signals in chronic pain states
- Respond to electrical stimuli[5]

Resting State
(Normal)



In Pain State
(Activated Glial Cell)

THE SYNAPTIC MICRO-ENVIRONMENT

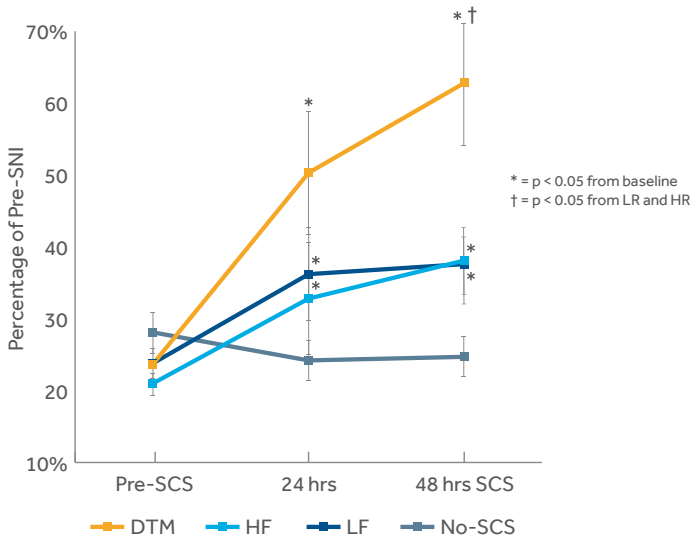


TOWARD A NEW THEORY

Hypothesis: Do glial and neuronal cells have varied responses to different waveforms?

Conclusion: In pre-clinical studies, the DTM™ waveform best modulates glial and neuronal gene expression **back toward the non-pain state.**[6-9]

MECHANICAL SENSITIVITY[8,9]



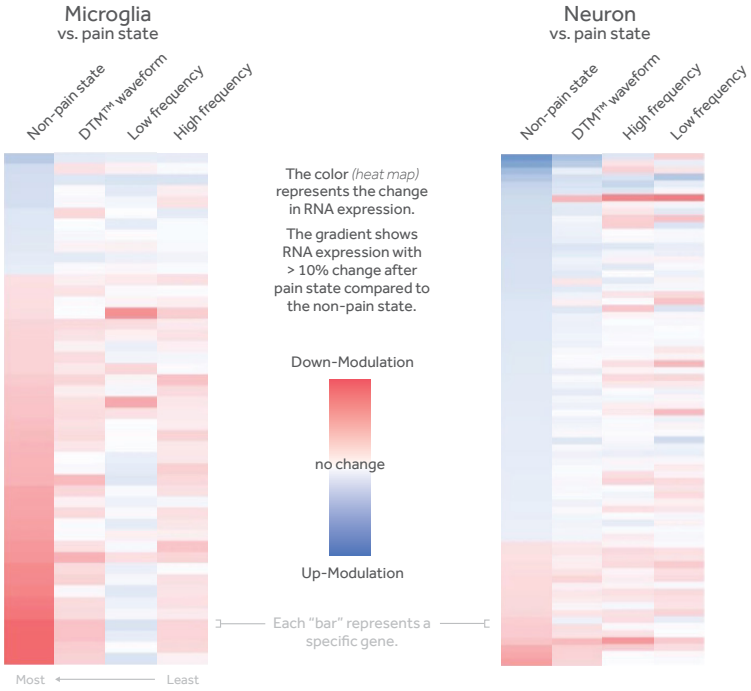
Evaluated SCS modalities:

- **DTM**
- **HF** = 1,200 Hz and PW = 50 µs
- **LF** = 50 Hz and PW = 150 µs

Study Description:
Behavioral studies were conducted in spared nerve injury (SNI) models of pain. Testing included post-acute withdrawal to a mechanical stimulus.

The DTM™ waveform has been studied in animal models, showing statistically significant reversal of pain behaviors compared to either low- or high-rate stimulation.[6,9,10]

GENE EXPRESSION ANALYSIS



Study Description:
Analysis of RNA expression comparing the pain state with non-pain state and SCS therapies.[6-9]

With the DTM™ waveform:

- **Glial cells were modulated, in addition to neurons.**
- **The neuron and microglia modulation was closest to non-pain state.**
- **Genes related to biological functions, such as neuroinflammation, were modulated toward the non-pain state.[9]**

INSPIRED BY SCIENCE

How is DTM™ SCS applied to your patient? DTM™ SCS is a proprietary, multiplexed algorithm coordinating multiple signals at multiple anatomical targets. Therapy and settings are customized to your individual patient's needs.

Patient selection[11]

- Patients diagnosed with back and leg pain, including unilateral pain (back/leg) *(≥ 5 cm VAS in low back pain with moderate to severe leg pain)*
- Diagnoses consistent with commercial labeling
- SCS naïve

DTM™ SCS proprietary algorithm includes:

3 THERAPY OPTIONS + **4** SIGNALS + **6** ANATOMICAL TARGETS + **6** PATIENT AMPLITUDES = DTM™ SCS PROGRAMMING ALGORITHM

Every DTM™ SCS therapy option coordinates multiple signals into one distinct therapy. The signals vary in frequency, pulse width, amplitude, and anatomical targets.

DTM™ SCS Workflow

Step-by-Step Process of Implementing DTM™ SCS Therapy

1. **IF** lead spans MID T8–MID T10, **THEN** consider the DTM™ SCS workflow.
2. **Patient flexion is recommended after lead placement** and before the final fluoro shot.
3. Use DTM™ SCS therapy, **a programming algorithm based on the coordination of multiple signals at multiple targets.**
4. **Conduct daily patient follow-up** to assess for optimal programming.

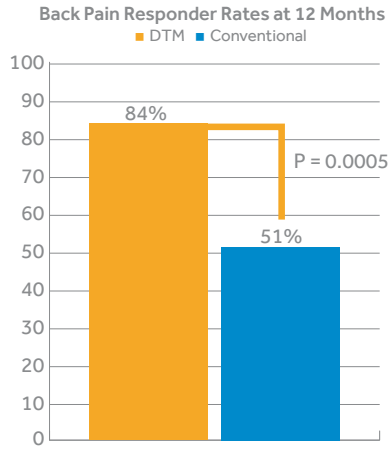
THE DTM SCS THERAPY IS PROVEN ONLY ON THE INTELLIS PLATFORM

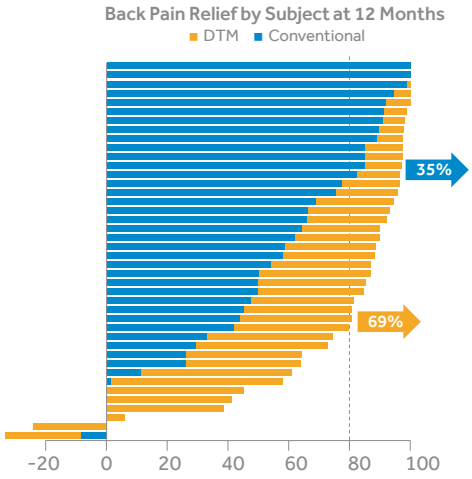
DTM™ SCS achieved superior back pain relief compared to conventional SCS at 3 and 12 months, with a therapy developed based on robust pre-clinical science.[11]

Post-market, multi-center, randomized control trial (RCT) comparing the efficacy of DTM™ SCS for back pain compared to conventional SCS using the Medtronic Intellis™ spinal cord stimulator.

84%

Highest back pain responder rate reported at 12 months in similar RCTs* *(> 50% improvement).*



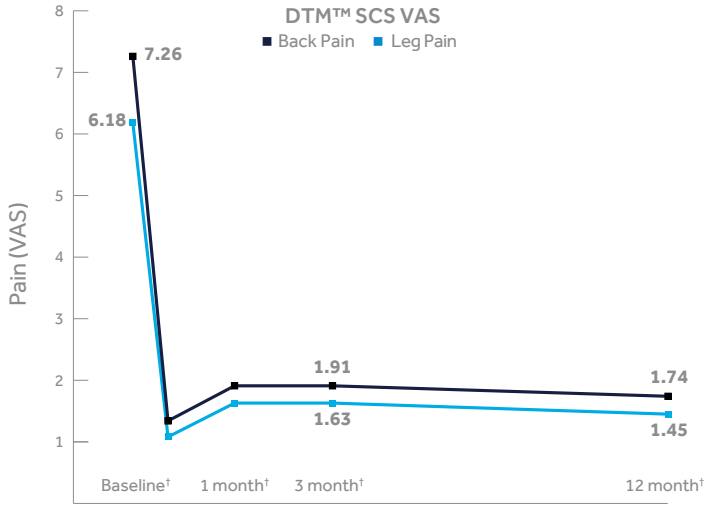


69%

7 out of 10 patients were profound back pain responders *(≥ 80% pain relief).*

** Descriptive comparison, including studies with similar design (RCT; randomization >100 subjects; comparing 2 SCS therapies; with at least 12-months follow up) and patient populations (inclusion/exclusion criteria; baseline demographics) with back pain responder rates reported. This is not based on a statistical analysis of outcomes between studies.*

Sustained back and leg pain relief with DTM™ SCS. **Mean VAS scores less than 2 at 12 months.**



7.26

with DTM™ SCS at 12 months

1.74

6.18

with DTM™ SCS at 12 months

1.45

† Back Pain (n): Baseline (58), 1 Month (46), 3 Month (47), 12 Month (43)
Leg Pain (n): Baseline (58), 1 Month (45), 3 Month (46), 12 Month (42)

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INDICATIONS Spinal cord stimulation (SCS) is indicated as an aid in the management of chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain. **CONTRAINDICATIONS Diathermy** - Energy from diathermy can be transferred through the implanted system and cause tissue damage resulting in severe injury or death. **WARNINGS** Sources of electromagnetic interference (e.g., defibrillation, electrocautery, MRI, RF ablation, and therapeutic ultrasound) can interact with the system, resulting in unexpected changes in stimulation, serious patient injury or death. An implanted cardiac device (e.g., pacemaker, defibrillator) may damage a neurostimulator, and electrical pulses from the neurostimulator may cause inappropriate response of the cardiac device. **PRECAUTIONS** Safety and effectiveness has not been established for pediatric use, pregnancy, unborn fetus, or delivery. Avoid activities that put stress on the implanted neurostimulation system components. Recharging a rechargeable neurostimulator may result in skin irritation or redness near the implant site. **ADVERSE EVENTS** May include: undesirable change in stimulation (uncomfortable, jolting or shocking); hematoma, epidural hemorrhage, paralysis, seroma, infection, erosion, device malfunction or migration, pain at implant site, loss of pain relief, and other surgical risks.
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