Appendix A: MYOBLOC REMS

MYOBLOC® (rimabotulinumtoxinB) Injection

BLA 103846

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S)

The goals of the REMS are to:

- minimize the risks of medication errors related to the lack of interchangeability of MYOBLOC units with those of toxins of other manufacturers; and
- inform prescribers and patients about the potential occurrence of spread of toxin effect beyond the injection site.

II. REMS ELEMENTS

A. Medication Guide

In compliance with 21 CFR 208.24, Solstice will institute the following measures:

Solstice will incorporate a Medication Guide for MYOBLOC that will be attached to the prescribing information (PI) with perforations allowing for easy separation from the PI by the healthcare professional administering MYOBLOC who will provide the tear-off guide to the patient. The revised PI with this attached Medication Guide will be packaged within each carton of MYOBLOC. In addition, Solstice will separately include accompanying Medication Guides formatted in a patient-focused brochure in a larger type size for easier readability by patients. Equal copies of the Medication Guides formatted in a patient-focused brochure will be packed in each carton/vial shipment of MYOBLOC.

B. Communication Plan

Solstice will implement a communication plan to healthcare providers to support implementation of the REMS. A Dear Healthcare Professional Letter (DHCPL) will be distributed with the FDA-approved labeling and Medication Guide for MYOBLOC to all neurologists and physiatrists.

The DHCPL will be mailed to all neurologists and physiatrists. The DHCPL package will be sent to the audience described above within 60 days of the final FDA-approval of the labeling.

The DHCPL is appended.

C. Elements to Assure Safe Use

The REMS for MYOBLOC does not require Elements to Assure Safe Use.

D. Implementation System

The REMS for MYOBLOC does not require an Implementation System.

E. Timetable for Submissions of Assessments

The timetable for Submission of Assessments is as follows:

- 1st Assessment: 18 months from REMS approval
- 2nd Assessment: 3 years from REMS approval
- 3rd Assessment: 7 years from REMS approval

MEDICATION GUIDE

Myobloc® (My-o-block)

(rimabotulinumtoxinB)

Injection

Read the Medication Guide that comes with MYOBLOC before you start using it and each time MYOBLOC is given to you. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. You should share this information with your family members and caregivers.

What is the most important information I should know about MYOBLOC?

MYOBLOC may cause serious side effects that can be life threatening. Call your doctor or get medical help right away if you have any of these problems after treatment with MYOBLOC:

- **Problems swallowing, speaking, or breathing. These problems can happen hours to weeks after an injection of MYOBLOC** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with MYOBLOC.

- People with certain breathing problems who need to use muscles in their neck to help them breathe may have more serious breathing problems with MYOBLOC.

- Swallowing problems may last for several months. People who can not swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving MYOBLOC have the highest risk of getting these problems.

- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
    - loss of strength and muscle weakness all over the body
    - double vision
    - blurred vision and drooping eyelids
    - hoarseness or change or loss of voice (dysphonia)
    - trouble saying words clearly (dysarthria)
    - loss of bladder control
    - trouble breathing
    - trouble swallowing

These symptoms can happen hours to weeks after you receive an injection of MYOBLOC.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving MYOBLOC?"

What is MYOBLOC?

MYOBLOC is a prescription medicine that is injected into muscles and used to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.

It is not known whether MYOBLOC is safe or effective in children.

It is not known whether MYOBLOC is safe or effective for other types of muscle spasms.

Who should not take MYOBLOC?

Do not take MYOBLOC if you:

- are allergic to MYOBLOC or any of the ingredients in MYOBLOC. See the end of this Medication Guide for a list of ingredients in MYOBLOC
- had an allergic reaction to any other botulinum toxin product such as Botox® or Dysport™
- have a skin infection at the planned injection site

What should I tell my doctor before taking MYOBLOC?

Tell your doctor about all your medical conditions, including if you have:

- a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis (ALS or Lou Gehrig's disease), myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about MYOBLOC?"
- allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- a breathing problem, such as asthma or emphysema
- swallowing problems
- bleeding problems
- plans to have surgery

Tell your doctor if you:

- are pregnant or plan to become pregnant. It is not known if MYOBLOC can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if MYOBLOC passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins and herbal products. Using MYOBLOC with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received MYOBLOC in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months
- have received injections of botulinum toxin, such as Botox®/Botox Cosmetic® (onabotulinumtoxinA) or Dysport™ (abobotulinumtoxinA) in the past; be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection
- take muscle relaxants
- take an allergy or cold medicine
- take a sleep medicine

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How should I take MYOBLOC?

- MYOBLOC is an injection that your doctor will give you.
- MYOBLOC is injected into the affected muscles.
- Your doctor may give you another dose of MYOBLOC after 12 weeks or longer, if it is needed.
- Your doctor may change your dose of MYOBLOC, until you and your doctor find the best dose for you.

What should I avoid while taking MYOBLOC?

MYOBLOC may cause loss of strength or general muscle weakness or vision problems within hours to weeks of taking MYOBLOC. If this happens, do not drive a car, operate machinery or do other dangerous activities. See "What is the most important information I should know about MYOBLOC?"

What are the possible side effects of MYOBLOC?

MYOBLOC can cause serious side effects. See "What is the most important information I should know about MYOBLOC?"

Other side effects of MYOBLOC include:

- dry mouth
- indigestion
- injection site discomfort or pain
- headache
- allergic reactions. Symptoms of an allergic reaction to MYOBLOC may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or fainting. Tell your doctor or get medical help right away if you get wheezing or asthma symptoms, or if you get dizzy or faint.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of MYOBLOC. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about MYOBLOC:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about MYOBLOC. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about MYOBLOC that is written for healthcare professionals. For more information about MYOBLOC call 1-888-461-2255 or go to www.MYOBLOC.com.

What are the ingredients in MYOBLOC?

Active ingredient: botulinum toxin type B

Inactive ingredients: human albumin, sodium succinate, and sodium chloride

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This Medication Guide has been approved by the U.S. Food and Drug Administration.

Distributed by: Solstice Neurosciences, Inc., South San Francisco, CA 94080

Myobloc® is a registered trademark of Solstice Neurosciences, Inc.

Botox® marks owned by Allergan, Inc.

Dysport™ is manufactured by Ipsen Biopharm Ltd.

IMPORTANT SAFETY INFORMATION

APPENDIX B: MYOBLOC Proposed REMS

Dear Healthcare Professional Letter

IMPORTANT SAFETY INFORMATION ABOUT MYOBLOC® (rimabotulinumtoxinB) INJECTION

Dear Healthcare Professional:

Solstice Neurosciences, Inc. ("Solstice") would like to inform you of 1) updated safety information regarding the risk of possible spread of botulinum toxin effects to sites distant from the injection site that appears in the prescribing information for Solstice's MYOBLOC as with all botulinum toxin products, 2) the introduction of a new established nonproprietary name for MYOBLOC, rimabotulinumtoxinB, that replaces the previous common nonproprietary name botulinum toxin type B, and 3) the introduction of a Risk Evaluation and Mitigation Strategy (REMS) that includes a Medication Guide for MYOBLOC to be provided to your patients receiving MYOBLOC.

The goals of the REMS are to:

- minimize the risks of medication errors related to the lack of interchangeability of MYOBLOC units with those of licensed botulinum toxins of other manufacturers; and
- inform prescribers and patients about the potential occurrence of spread of toxin effect beyond the injection site.

You are advised to discuss the risks associated with MYOBLOC therapy outlined in the enclosed Medication Guide for MYOBLOC and Dear Healthcare Professional Letter with anyone in your practice who is involved in the preparation, prescribing and/or injection of MYOBLOC.

Per FDA regulations, a copy of the Medication Guide for MYOBLOC must be distributed directly to each patient every time he/she receives a MYOBLOC injection. Copies of this Medication Guide for MYOBLOC are enclosed and if you wish to obtain additional copies of the Medication Guide for distribution to your patients please call 1-888-461-2255 or download a copy at www.myobloc.com/medguide. A copy of the Medication Guide will also be present in every carton of MYOBLOC. Permission is granted to prescribers to reproduce Medication Guides as needed.

Botulinum toxin products are not interchangeable

Because there are currently multiple marketed botulinum toxin products with different dose to potency ratios, there is a concern about medication errors such as overdosing based on incorrect unit administration from interchanging the products. It is important to understand that **MYOBLOC®** (rimabotulinumtoxinB), BOTOX®/BOTOX® Cosmetic (onabotulinumtoxinA, Allergan, Inc.), and DYSPORT™ (abobotulinumtoxinA, Ipsen Biopharm Limited/Medicis Corporation) are unique biologic products that are **not interchangeable** with each other.

Therefore, the units of biological activity of MYOBLOC cannot be compared to nor converted into units of any other botulinum toxin product. Caution should be taken to ensure that the dosing, dilution, injection volume, and injection pattern are appropriate for the product.

Information on the lack of interchangeability between the botulinum toxin products (WARNINGS: Lack of Interchangeability between Botulinum Toxin Products) is provided in the enclosed copy of the FDA-approved MYOBLOC Full Prescribing Information as well as below.

Lack of Interchangeability between Botulinum Toxin Products

The potency units of MYOBLOC 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 MYOBLOC cannot be compared to or converted into units of any other botulinum toxin products assessed with any other specific assay method (see DESCRIPTION)**.**

Other changes have been made in the CLINICAL PHARMACOLOGY and OVERDOSAGE sections of the prescribing information.

To help differentiate these products and address the concern for medication errors and non-interchangeability of the multiple botulinum toxin products, Solstice, in conjunction with the Food and Drug Administration and the United States Adopted Names Council, has adopted the established name rimabotulinumtoxinB that is specific to MYOBLOC. This uniquely established nonproprietary name replaces the previous common term Botulinum Toxin Type B. Nothing about Solstice's unique MYOBLOC product, its formulation or approved uses have been changed in conjunction with the change in nonproprietary name. The change in the nonproprietary name for MYOBLOC will enable continued tracking of product for patient safety purposes and addresses the challenges healthcare practitioners may face in distinguishing information, long associated with MYOBLOC**,** with that of other toxin products.

Risk of possible spread of botulinum toxin

Information on the spread of toxin effect (BOXED WARNING and WARNINGS: Spread of Toxin Effect, Pre-existing Neuromuscular Disorders, Dysphagia and Breathing Difficulties in the Treatment of Cervical Dystonia; PRECAUTIONS: Information for Patients) is provided in the enclosed copy of the FDA-approved MYOBLOC Full Prescribing Information as well as below.

DISTANT SPREAD OF TOXIN EFFECT—Spread of Toxin Effect

Postmarketing safety reports from MYOBLOC and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and 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 related to spread of toxin effects. 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, and particularly in those patients who have underlying conditions that would predispose them to these symptoms. In unapproved uses, including spasticity in children and adults, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia.

Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with MYOBLOC 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 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 months, 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.

Treatment of cervical dystonia with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure, in cervical dystonia patients. 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 (see ADVERSE REACTIONS, CLINICAL PHARMACOLOGY).

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional 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 MYOBLOC (see ADVERSE REACTIONS).

INFORMATION FOR PATIENTS

The physician should provide a copy of the FDA-Approved Patient Medication Guide and review the contents with the patient. Patients should be advised to inform their doctor or pharmacist if

they develop any unusual symptoms (including difficulty with swallowing, speaking or breathing), or if any existing symptom worsens.

Patients should be counseled that if loss of strength, muscle weakness, or impaired vision occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Please carefully review this information and the revised labeling including the Medication Guide which are enclosed. Contact Solstice Medical Affairs at 1-888-461-2255 if you have any questions about this information or the safe and effective use of MYOBLOC.

We also encourage you to report any adverse events experienced by your patients. Call Solstice at 1-888-461-2255 to report adverse events occurring in connection with use of MYOBLOC. Alternatively, this information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or by mail using the Form 3500 at http://www.fda.gov/medwatch/index/html.

The revised product information, including the Medication Guide, will be included with shipments of MYOBLOC (rimabotulinumtoxinB) Injection and are also available on the product website www.myobloc.com or by contacting Medical Information at 1-888-461-2255 8:00 am to 7:00 pm Eastern Time, Monday-Friday. Call this number for any other questions about clinical use or dosing of MYOBLOC.

Sincerely,

Robert Chinnapongse, MD

Medical Director

Solstice Neurosciences, Inc.

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