

# Myobloc<sup>®</sup> (rimabotulinumtoxinB) Injection

## Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of MYOBLOC 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, including spasticity in children and adults, and in approved indications, cases of spread of effect have occurred at doses comparable to those used to treat cervical dystonia and at lower doses.

## DESCRIPTION

Myobloc<sup>®</sup> (rimabotulinumtoxinB) injection is a sterile liquid formulation of a purified neurotoxin that acts at the neuromuscular junction to produce flaccid paralysis. The neurotoxin is produced by fermentation of the bacterium *Clostridium botulinum* type B (Bean strain) and exists in noncovalent association with hemagglutinin and nonhemagglutinin proteins as a neurotoxin complex. The neurotoxin complex is recovered from the fermentation process and purified through a series of precipitation and chromatography steps.

MYOBLOC is provided as a clear and colorless to light-yellow sterile injectable solution in 3.5-mL glass vials. Each single-use vial of formulated MYOBLOC contains 5,000 Units of botulinum toxin type B per milliliter in 0.05% human serum albumin, 0.01 M sodium succinate, and 0.1 M sodium chloride at approximately pH 5.6.

One unit of MYOBLOC corresponds to the calculated median lethal intraperitoneal dose (LD50) in mice. The method for performing the assay is specific to Solstice Neurosciences' manufacture of MYOBLOC. Due to differences in specific details such as the vehicle, dilution scheme and laboratory protocols for various mouse LD50 assays, units of biological activity of MYOBLOC cannot be compared to or converted into units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species sensitivities to different botulinum neurotoxin serotypes preclude extrapolation of animal dose-activity relationships to human dose estimates. The specific activity of MYOBLOC ranges between 70 to 130 Units/ng.

## CLINICAL PHARMACOLOGY

The seven serologically distinct botulinum neurotoxins, designated A through G, share a common structural organization consisting of one Heavy Chain and one Light Chain polypeptide linked by a single disulfide bond. These toxins inhibit acetylcholine release at the neuromuscular junction via a three stage process: 1) Heavy Chain mediated neurospecific binding of the toxin, 2) internalization of the toxin by receptor-mediated endocytosis, and 3) ATP and pH dependent translocation of the Light Chain to the neuronal cytosol where it acts as a zinc-dependent endoprotease cleaving polypeptides essential for neurotransmitter release. MYOBLOC specifically has been demonstrated to cleave synaptic Vesicle Associated Membrane Protein

(VAMP, also known as synaptobrevin) which is a component of the protein complex responsible for docking and fusion of the synaptic vesicle to the presynaptic membrane, a necessary step to neurotransmitter release.

### **PHARMACOKINETICS**

Using currently available analytical technology, it is not possible to detect MYOBLOC in the peripheral blood following intramuscular injection at the recommended doses.

### **CLINICAL STUDIES**

Two phase 3, randomized, multi-center, double-blind, placebo controlled studies of the treatment of cervical dystonia were conducted. Both studies enrolled only adult patients who had a history of receiving botulinum toxin type A in an open label manner, with a perceived good response and tolerable adverse effects. Study #301 enrolled patients who were perceived as having an acceptable response to type A toxin, while Study #302 enrolled only patients who had secondarily lost responsiveness to type A toxin. Other eligibility criteria common to both studies were that all subjects had moderate or greater severity of cervical dystonia with at least 2 muscles involved, no neck contractures or other causes of decreased neck range of motion, and no history of any other neuromuscular disorder. Subjects in Study #301 were randomized to receive placebo, 5,000 Units or 10,000 Units of MYOBLOC, and subjects in Study #302 were randomized to receive placebo or 10,000 Units of MYOBLOC. Study agent was administered to subjects in a single treatment session by investigators who selected 2 to 4 muscles per subject from the following: Splenius capitis, Sternocleidomastoid, Levator scapulae, Trapezius, Semispinalis capitis, and Scalene muscles. The total dose was divided between the selected muscles, and from 1 to 5 injections were made per muscle. There were 109 subjects enrolled into Study #301, and 77 into Study #302. Patient evaluations continued for 16 weeks post injection.

The primary efficacy outcome variable for both studies was the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total Score (scale range of possible scores is 0–87) at Week 4. TWSTRS is comprised of three sub-scales which examine 1) Severity—the severity of the patient's abnormal head position; 2) Pain—the severity and duration of pain due to the dystonia; and 3) Disability—the effects of the abnormal head position and pain on a patient's activities. The secondary endpoints were the Patient Global and Physician Global Assessments of change at Week 4. Both Global Assessments used a 100-point visual-analog scale (VAS). The Patient Global Assessment allows patients to indicate how they feel at the time of their evaluation compared to the pre-injection baseline. Likewise, the Physician Global Assessment indicates the physician's assessment of a patient's change from baseline to Week 4. Scores of 50 indicate no change, 0 much worse, and 100 much better. Results of comparisons of the primary and secondary efficacy variables are summarized in Table 1.

**Table 1—Efficacy Results From Two Phase 3 MYOBLOC Studies**

| Assessments*            | STUDY 301         |                          |                           | STUDY 302         |                           |
|-------------------------|-------------------|--------------------------|---------------------------|-------------------|---------------------------|
|                         | Placebo<br>n = 36 | 5,000<br>Units<br>n = 36 | 10,000<br>Units<br>n = 37 | Placebo<br>n = 38 | 10,000<br>Units<br>n = 39 |
| <b>TWSTRS Total</b>     |                   |                          |                           |                   |                           |
| Mean at Baseline        | 43.6              | 46.4                     | 46.9                      | 51.2              | 52.8                      |
| Change from Baseline    | -4.3              | -9.3                     | -11.7                     | -2.0              | -11.1                     |
| 95% Confidence Interval |                   | (-8.9, -1.2)             | (-11.1, -3.3)             |                   | (-12.2, -5.2)             |
| <i>P</i> value          |                   | 0.012                    | 0.0004                    |                   | 0.0001                    |
| <b>Patient Global</b>   |                   |                          |                           |                   |                           |
| Mean at Week Four       | 43.6              | 60.6                     | 64.6                      | 39.5              | 60.2                      |
| 95% Confidence Interval |                   | (7.0, 26.9)              | (11.3, 31.1)              |                   | (11.2, 29.1)              |
| <i>P</i> value          |                   | 0.001                    | 0.0001                    |                   | 0.0001                    |
| <b>Physician Global</b> |                   |                          |                           |                   |                           |
| Mean at Week Four       | 52.0              | 65.3                     | 64.2                      | 47.9              | 60.6                      |
| 95% Confidence Interval |                   | (5.5, 21.3)              | (3.9, 19.7)               |                   | (7.4, 18.1)               |
| <i>P</i> value          |                   | 0.001                    | 0.004                     |                   | 0.0001                    |
| <b>TWSTRS-Subscales</b> |                   |                          |                           |                   |                           |
| <b>- Severity</b>       |                   |                          |                           |                   |                           |
| Mean at Baseline        | 18.4              | 20.2                     | 20.2                      | 22.1              | 22.6                      |
| Change from Baseline    | -2.3              | -3.2                     | -4.8                      | -1.2              | -3.7                      |
| 95% Confidence Interval |                   | (-2.5, 0.6)              | (-4.0, -1.0)              |                   | (-3.9, -1.0)              |
| <i>P</i> value          |                   | 0.22                     | 0.002                     |                   | 0.001                     |
| <b>- Pain</b>           |                   |                          |                           |                   |                           |
| Mean at Baseline        | 10.9              | 11.8                     | 12.4                      | 12.2              | 11.9                      |
| Change from Baseline    | -0.5              | -3.6                     | -4.2                      | -0.2              | -3.6                      |
| 95% Confidence Interval |                   | (-4.7, -1.1)             | (-5.1, -1.4)              |                   | (-5.0, -2.1)              |
| <i>P</i> value          |                   | 0.002                    | 0.0008                    |                   | 0.0001                    |
| <b>- Disability</b>     |                   |                          |                           |                   |                           |
| Mean at Baseline        | 14.3              | 14.4                     | 14.4                      | 16.9              | 18.3                      |
| Change from Baseline    | -1.6              | -2.5                     | -2.7                      | 0.8               | -3.8                      |
| 95% Confidence Interval |                   | (-2.7, 0.7)              | (-2.8, 0.6)               |                   | (-4.1, -1.0)              |
| <i>P</i> value          |                   | 0.26                     | 0.19                      |                   | 0.002                     |

\* 95% CI are for the differences between the active and placebo groups. The *P* values are for the comparison of active dose and placebo. For TWSTRS-Total and TWSTRS-subscale scores, *P* values are from ANCOVA for each variable with center and treatment in the model and the baseline value of the variable included as a covariate. For the Patient Global and Physician Global Assessments, *P* values are from ANOVA for each variable with center and treatment in the model.

There were no statistically significant differences in results between the 5,000 Units and 10,000 Units doses in Study #301. Exploratory analyses of these two studies suggested that the majority of patients who showed a beneficial response by Week 4 had returned to their baseline status between Weeks 12 to 16 post injection. Although there was a MYOBLOC associated decrease in pain, there remained many patients who experienced an increase in dystonia-related neck pain irrespective of treatment group (see **ADVERSE REACTIONS**). TWSTRS Total Score at Week 4 and Patient Global Assessment among subgroups by gender or age showed consistent treatment-associated effects across these subgroups (see also **PRECAUTIONS: GERIATRICS**).

There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

MYOBLOC was studied in two phase 2 dose ranging studies, Studies #08 and #09, which preceded the phase 3 studies. Studies #08 and #09 had a study design similar to the phase 3 studies, including eligibility criteria. Study #08 enrolled 85 subjects randomized between doses of placebo, 400 Units, 1,200 Units, or 2,400 Units (21 or 22 subjects per group). Study #09 enrolled 122 subjects and randomized between doses of placebo, 2,500 Units, 5,000 Units, and 10,000 Units (30 or 31 subjects per group). These studies demonstrated efficacy on the TWSTRS-Total, baseline to Week 4, at doses of 2,400 Units, 2,500 Units, 5,000 Units, and 10,000 Units. Study #08 showed mean improvement from baseline on the Week 4 TWSTRS for placebo and 2,400 Units of 2.0 and 8.5 points respectively (from baselines of 42.0 and 42.4 points). Study #09 showed mean improvement from baseline to Week 4 for placebo, 2,500 Units, 5,000 Units, and 10,000 Units of 3.3, 11.6, 12.5, and 16.4 points, respectively (from baselines of 45.5, 45.6, 45.2, and 47.5 points). Study #08 also indicated there is less response for doses below 2,400 Units.

Study #352 was an open label, inpatient dose-escalation study of 3 treatment sessions where each patient with cervical dystonia sequentially received 10,000 Units, 12,500 Units, and 15,000 Units, at periods of 12 to 16 weeks between treatment sessions irrespective of their response to their previous dose. This study enrolled 145 patients, of whom 125 received all three treatments. Although this was an open label design where investigators and patients knew the dose at each treatment session, there were similar mean improvements on the TWSTRS-Total, from baseline to Week 4, for all three doses.

In the MYOBLOC injected patients (n=112) of the phase 3 studies, 19% had 2 muscles injected, 48% had 3 muscles injected, and 33% had 4 muscles injected. Table 2 indicates the frequency of use for each of the permitted muscles, and the fraction of the total dose of the treatment injected into each muscle, for those patients in whom the muscle was injected.

**Table 2—Studies 301 and 302 Combined Data Fraction of Total Dose Injected into Involved Muscles**

| Muscle Injected      | Percent Frequency Injected* | Fraction of Total Dose Injected by Percentiles |      |      |
|----------------------|-----------------------------|--|------|------|
|                      |                             | 25th   | 50th | 75th |
| Splenius Capitis     | 88                          | 0.30   | 0.40 | 0.50 |
| Sternocleidomastoid  | 80                          | 0.20   | 0.25 | 0.30 |
| Semispinalis Capitis | 52                          | 0.30   | 0.36 | 0.50 |
| Levator Scapulae     | 46                          | 0.13   | 0.20 | 0.20 |
| Trapezius            | 38                          | 0.20   | 0.25 | 0.35 |
| Scalene Complex      | 13                          | 0.20   | 0.25 | 0.30 |

\* Percent frequency of patients in whom each muscle was injected

## INDICATIONS AND USAGE

MYOBLOC 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.

## **CONTRAINDICATIONS**

MYOBLOC is contraindicated in patients with a known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

MYOBLOC is contraindicated for use in patients with infection at the proposed injection site(s).

## **WARNINGS**

### **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).**

### **Spread of Toxin Effect**

Postmarketing safety data 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**).

## **Pre-Existing Neuromuscular Disorders**

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**).

## **Human Albumin**

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. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

## **PRECAUTIONS**

Only 9 subjects without a prior history of tolerating injections of type A botulinum toxin have been studied. Treatment of botulinum toxin naïve patients should be initiated at lower doses of MYOBLOC (see **ADVERSE REACTIONS: Overview**).

## **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.

## **DRUG INTERACTIONS**

Co-administration of MYOBLOC and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

The effect of administering different botulinum neurotoxin serotypes at the same time or within less than 4 months of each other is unknown. However, neuromuscular paralysis may be potentiated by co-administration or overlapping administration of different botulinum toxin serotypes.

## **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**

No long-term carcinogenicity studies in animals have been performed.

## **PREGNANCY**

**PREGNANCY CATEGORY C.** Animal reproduction studies have not been conducted with MYOBLOC. It is also not known whether MYOBLOC can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. MYOBLOC should be given to a pregnant woman only if clearly needed.

## **NURSING MOTHERS**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MYOBLOC is administered to a nursing woman.

## **PEDIATRIC USE**

Safety and effectiveness in pediatric patients have not been established.

## **GERIATRIC USE**

In the controlled studies summarized in **CLINICAL STUDIES**, for MYOBLOC treated patients, 152 (74.5%) were under the age of 65, and 52 (25.5%) were aged 65 or greater. For these age groups, the most frequent reported adverse events occurred at similar rates in both age groups. Efficacy results did not suggest any large differences between these age groups.

Very few patients aged 75 or greater were enrolled, therefore no conclusions regarding the safety and efficacy of MYOBLOC within this age group can be determined.

## **ADVERSE REACTIONS**

### **Overview**

The most commonly reported adverse events associated with MYOBLOC treatment in all studies were dry mouth, dysphagia, dyspepsia, and injection site pain. Dry mouth and dysphagia were the adverse reactions most frequently resulting in discontinuation of treatment. There was an increased incidence of dysphagia with increased dose in the sternocleidomastoid muscle. The incidence of dry mouth showed some dose-related increase with doses injected into the splenius capitis, trapezius and sternocleidomastoid muscles.

Only nine subjects without a prior history of tolerating injections of type A botulinum toxin have been studied. Adverse event rates have not been adequately evaluated in these patients, and may be higher than those described in Table 3.

### **Discussion**

Adverse reaction rates observed in the clinical trials for a product cannot be directly compared to rates in clinical trials for another product and may not reflect the rates observed in actual clinical practice. However, adverse reaction information from clinical trials does provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

MYOBLOC was studied in both placebo controlled single treatment studies and uncontrolled repeated treatment studies; most treatment sessions and patients were in the uncontrolled studies. The data described below reflect exposure to MYOBLOC at varying doses in 570 subjects, including more than 300 patients with 4 or more treatment sessions. Most treatment sessions were at doses of 12,500 Units or less. There were 57 patients administered a dose of 20,000 or 25,000 Units. All but nine patients had a prior history of receiving type A botulinum toxin and adequately tolerating the treatment to have received repeated doses.

The rates of adverse events and association with MYOBLOC are best assessed in the results from the placebo controlled studies of a single treatment session with active monitoring. The data in Table 3 reflect those adverse events occurring in at least 5% of patients exposed to MYOBLOC treatment in pooled placebo controlled clinical trials. Annual rates of adverse events are higher in the overall data which includes longer duration follow-up of patients with repeated treatment experience. The mean age of the population in these studies was 55-years-old with approximately 66% being female. Most of the patients studied were Caucasian and all had cervical dystonia that was rated as moderate to severe in severity.

**Table 3—Treatment-Emergent AEs Reported by at Least 5% of MYOBLOC Treated Patients by Dose Group, Following Single Treatment Session in Controlled Studies 09, 301 and 302**

| Adverse Event<br>(COSTART Term)   | Placebo<br>(N=104) | Dosing Groups            |                          |                            |
|-----------------------------------|--------------------|--------------------------|--------------------------|----------------------------|
|                                   |                    | 2,500<br>Units<br>(N=31) | 5,000<br>Units<br>(N=67) | 10,000<br>Units<br>(N=106) |
| Dry Mouth                         | 3 (3%)             | 1 (3%)                   | 8 (12%)                  | 36 (34%)                   |
| Dysphagia                         | 3 (3%)             | 5 (16%)                  | 7 (10%)                  | 27 (25%)                   |
| Neck Pain related to<br>CD*       | 17 (16%)           | 0 (0%) <sup>†</sup>      | 11 (16%)                 | 18 (17%)                   |
| Injection Site Pain               | 9 (9%)             | 5 (16%)                  | 8 (12%)                  | 16 (15%)                   |
| Infection                         | 16 (15%)           | 4 (13%)                  | 13 (19%)                 | 16 (15%)                   |
| Pain                              | 10 (10%)           | 2 (6%)                   | 4 (6%)                   | 14 (13%)                   |
| Headache                          | 8 (8%)             | 3 (10%)                  | 11(16%)                  | 12 (11%)                   |
| Dyspepsia                         | 5 (5%)             | 1 (3%)                   | 0 (0%)                   | 11(10%)                    |
| Nausea                            | 5 (5%)             | 3 (10%)                  | 2 (3%)                   | 9 (8%)                     |
| Flu Syndrome                      | 4 (4%)             | 2 (6%)                   | 6 (9%)                   | 9 (8%)                     |
| Torticollis                       | 7 (7%)             | 0 (0%)                   | 3 (4%)                   | 9 (8%)                     |
| Pain Related to<br>CD/Torticollis | 4 (4%)             | 3 (10%)                  | 3 (4%)                   | 7 (7%)                     |
| Arthralgia                        | 5 (5%)             | 0 (0%)                   | 1 (1%)                   | 7 (7%)                     |
| Back Pain                         | 3 (3%)             | 1 (3%)                   | 3 (4%)                   | 7 (7%)                     |
| Cough Increased                   | 3 (3%)             | 1 (3%)                   | 4 (6%)                   | 7 (7%)                     |
| Myasthenia                        | 3 (3%)             | 1 (3%)                   | 3 (4%)                   | 6 (6%)                     |
| Asthenia                          | 4 (4%)             | 1 (3%)                   | 0 (0%)                   | 6 (6%)                     |
| Dizziness                         | 2 (2%)             | 1 (3%)                   | 2 (3%)                   | 6 (6%)                     |
| Accidental Injury                 | 4 (4%)             | 0 (0%)                   | 3 (4%)                   | 5 (5%)                     |
| Rhinitis                          | 6 (6%)             | 1 (3%)                   | 1 (1%)                   | 5 (5%)                     |

\* Not a COSTART term

<sup>†</sup> Not collected in Study 09 by special COSTART term

In the overall clinical trial experience with MYOBLOC (570 patients, including the uncontrolled studies), most cases of dry mouth or dysphagia were reported as mild or moderate in severity. Severe dysphagia was reported by 3% of patients. Severe dry mouth was reported by 6% of patients. Dysphagia and dry mouth were the most frequent adverse events reported as a reason for discontinuation from repeated treatment studies. These adverse events led to discontinuation from further treatments with MYOBLOC in some patients even when not reported as severe.

The following additional adverse events were reported in 2% or greater of patients participating in any of the clinical studies (COSTART terms, by body system):

*Body as a Whole:* allergic reaction, fever, headache related to injection, chest pain, chills, hernia, malaise, abscess, cyst, neoplasm, viral infection; *Musculoskeletal:* arthritis, joint disorder; *Cardiovascular System:* migraine; *Respiratory:* dyspnea, lung disorder, pneumonia; *Nervous System:* anxiety, tremor, hyperesthesia, somnolence, confusion, pain related to CD/torticollis, vertigo, vasodilation; *Digestive System:* gastrointestinal disorder, vomiting, glossitis, stomatitis, tooth disorder; *Skin and Appendages:* pruritis; *Urogenital System:* urinary tract infection, cystitis, vaginal moniliasis; *Special Senses:* amblyopia, otitis media, abnormal vision, taste perversion, tinnitus; *Metabolic and Nutritional Disorders:* peripheral edema, edema, hypercholesterolemia; *Hemic and Lymphatic System:* ecchymosis.



## Postmarketing

The following adverse events have been reported during postmarketing use for approved and unapproved indications: angioedema, urticaria, rash and constipation.

## Immunogenicity

A two-stage assay was used to test for immunogenicity and neutralizing activity induced by treatment with MYOBLOC. In order to account for varying lengths of follow-up, life-table analysis methods were used to estimate the rates of development of immune responses and neutralizing activity. During the repeated treatment studies, 446 subjects were followed with periodic ELISA based evaluations for development of antibody responses against MYOBLOC. Only patients who showed a positive ELISA assay were subsequently tested for the presence of neutralizing activity against MYOBLOC in the mouse neutralization assay (MNA). 12% of patients had positive ELISA assays at baseline. Patients began to develop new ELISA responses after a single treatment session with MYOBLOC. By six months after initiating treatment, estimates for ELISA positive rate were 20%, which continued to rise to 36% at one year and 50% positive ELISA status at 18 months. Serum neutralizing activity was primarily not seen in patients until after 6 months. Estimated rates of development were 10% at one year and 18% at 18 months in the overall group of patients, based on analysis of samples from ELISA positive individuals. The effect of conversion to ELISA or MNA positive status on efficacy was not evaluated in these studies, and the clinical significance of development of antibodies has not been determined.

The data reflect the percentage of patients whose test results were considered positive for antibodies to MYOBLOC in both an *in vitro* and *in vivo* assay. The results of these antibody tests are highly dependent on the sensitivity and specificity of the assays. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to MYOBLOC with the incidence of antibodies to other products may be misleading.

## OVERDOSAGE

Excessive doses of MYOBLOC may be expected to produce neuromuscular weakness with a variety of symptoms. Respiratory support may be required where excessive doses cause paralysis of respiratory muscles. In the event of overdose, the patient should be medically monitored for symptoms of excessive muscle weakness or muscle paralysis (see **WARNINGS** and **PRECAUTIONS**). Symptomatic treatment may be necessary.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur, the person should be medically supervised for several weeks for signs and symptoms of excessive muscle weakness or muscle paralysis.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 770-488-7100. More information can be obtained at <http://cdc.gov/ncidod/srp/drugs/drug-service.html>.

## DOSAGE AND ADMINISTRATION

The recommended initial dose of MYOBLOC for patients with a prior history of tolerating botulinum toxin injections is 2,500 to 5,000 Units divided among affected muscles (see **CLINICAL**

**STUDIES**). Patients without a prior history of tolerating botulinum toxin injections should receive a lower initial dose. Subsequent dosing should be optimized according to the patient's individual response. MYOBLOC should be administered by physicians familiar and experienced in the assessment and management of patients with CD.

The method described for performing the potency assay is specific to Solstice Neurosciences' manufacture of MYOBLOC. Due to differences in the specific details of this assay such as the vehicle, dilution scheme and laboratory protocols for various potency assays, Units of biological activity of MYOBLOC cannot be compared to or converted into units of any other botulinum toxin or any toxin assessed with any other specific assay method. Therefore, differences in species' sensitivities to different botulinum neurotoxin serotypes preclude extrapolation of animal dose-activity relationships to human dose estimates.

The duration of effect in patients responding to MYOBLOC treatment has been observed in studies to be between 12 and 16 weeks at doses of 5,000 Units or 10,000 Units (see **CLINICAL STUDIES**).

### **HOW SUPPLIED**

MYOBLOC is provided as a clear and colorless to light-yellow sterile injectable solution in single-use 3.5-mL glass vials. Each single-use vial of formulated MYOBLOC contains 5,000 Units<sup>a</sup> of botulinum toxin type B per milliliter in 0.05% human serum albumin, 0.01 M sodium succinate, 0.1 M sodium chloride at approximately pH 5.6.

<sup>a</sup> See **DOSAGE AND ADMINISTRATION**

MYOBLOC is available in the following three presentations.

| <b>Dosage Strength</b> | <b>Volume Per Vial</b> | <b>Single-Vial Carton</b> |
|------------------------|------------------------|---------------------------|
| 2,500 Units            | 0.5 mL                 | NDC 10454-710-10          |
| 5,000 Units            | 1 mL                   | NDC 10454-711-10          |
| 10,000 Units           | 2 mL                   | NDC 10454-712-10          |

Store under refrigeration at 2°- 8°C (36°- 46°F).

**DO NOT FREEZE. DO NOT SHAKE.**

**Protect from light. No U.S. Standard of Potency.**

**Ready to use; no reconstitution required.** The recommended storage condition for MYOBLOC is refrigeration at 2°- 8°C.

MYOBLOC may be diluted with normal saline. Once diluted, the product must be used within 4 hours as the formulation does not contain a preservative.

All vials of expired MYOBLOC and equipment used in the administration of MYOBLOC should be carefully discarded according to standard medical waste practices.

Do not use after the expiration date stamped on the vial.

**Discard unused portion.**

**Single-use vial.**

**Rx ONLY**

Manufactured By:  
Solstice Neurosciences, Inc., South San Francisco, CA 94080

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