Product Monograph

MYOBLOC®

(Botulinum Toxin Type B)

5000 Units/mL

Sterile Solution for Intramuscular Injection

Neuromuscular Blocking Agent

Solstice NeuroSciences, LLC
3830 Valley Centre Drive, Suite 705-5
San Diego, CA
92130

Control #: 093208

Date of Preparation:
August 09, 2004

Product Monograph

NAME OF DRUG

MYOBLOC® (Botulinum Toxin Type B)

5000 Units/mL; Sterile Solution for Intramuscular Injection

THERAPEUTIC CLASSIFICATION

Neuromuscular Blocking Agent

ACTION AND CLINICAL PHARMACOLOGY

The mechanism of action of Botulinum Toxin Type B in blocking the release of acetylcholine (ACh) at the neuromuscular junction is believed to occur by a three step process: 1) extracellular binding of the toxin to specific acceptors on the motor nerve terminals; 2) internalization and release of the toxin into the cytosol of the nerve terminals; and 3) inhibition of ACh release from nerve terminals at the neuromuscular junction.

There are eight antigenically distinct Botulinum serotypes: A, B, C_1, C_2, D, E, F, and G. All are neurotoxins except serotype C_2. These neurotoxins are zinc-dependent endopeptidases that target and cleave different intracellular proteins (1). These targeted cellular proteins are part of the intracellular docking proteins responsible for the release of ACh from synaptic vesicles into the neuromuscular junction. Botulinum Toxin

Type A cleaves (SNAP-25) whereas Type B cleaves Vesicle-Associated Membrane Protein (VAMP, also known as synaptobrevin), (1,2,3) resulting in an inhibition of ACh release and localized muscle weakness (paresis/paralysis) that gradually reverses over time. The precise mechanism by which Botulinum Toxin-induced muscle weakness is reversed is unknown.

There are no known antibodies that cross-react with and neutralize both Type A and Type B neurotoxins. These results support the general observation that neutralizing antibodies for one Botulinum Toxin serotype do not neutralize the activity of Botulinum Toxin of other serotypes (3,4).

Botulinum Toxin Type B injected intramuscularly (IM) produces localized muscle weakness by chemical denervation. Following local IM injection at the recommended doses, Botulinum Toxin Type B is not expected to be present in the peripheral blood at measureable levels. Pharmacokinetic or absorption, distribution, metabolism, and elimination studies were not performed.

INDICATIONS AND CLINICAL USE

MYOBLOC® (Botulinum Toxin Type B) is indicated for the treatment of adult patients with cervical dystonia (CD). In addition, MYOBLOC® is indicated for the management of adult patients with cervical dystonia who are resistant to Type A toxin. MYOBLOC® treatment reduces the pain, disability, and severity of dystonia, resulting in overall patient improvement.

CONTRAINDICATIONS

MYOBLOC® (Botulinum Toxin Type B) is contraindicated in patients with neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) and in those

with a known hypersensitivity to any ingredient in the formulation. Formulated MYOBLOC® contains Botulinum Toxin Type B, human serum albumin (FDA released), sodium succinate, and sodium chloride.

WARNINGS

The dosage and frequency of administration of MYOBLOC® (Botulinum Toxin Type B), as described under **DOSAGE AND ADMINISTRATION**, should not be exceeded. Risks resulting from administration at higher dosages or at increased frequency are not known.

Co-administration of MYOBLOC® and aminoglycosides or other anitbiotics, including tetracycline, or 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.

Individuals with known neuromuscular diseases (e.g., ALS, peripheral neuropathy) should only receive MYOBLOC® with caution.

There were no documented cases of botulism resulting from the IM injection of MYOBLOC® in patients with CD treated in clinical trials. If, however, botulism is clinically suspected, hospitalization for the monitoring of systemic weakness or paralysis and respiratory function (incipient respiratory failure) may be required.

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

PRECAUTIONS

DRUG INTERACTIONS

Clinical studies have not directly addressed the effect of administering different Botulinum neurotoxin serotypes at the same time or within less than 4 months of each other. However, neuromuscular paralysis may be potentiated by co-administration or overlapping administration of different Botulinum toxin serotypes. (See **WARNINGS.**)

As with any injection of a protein therapeutic, there is potential for anaphylactic reaction. Although such an event is extremely unlikely, the clinician should have epinephrine or alternative aids readily available

PREGNANCY

There are no adequate and well-controlled studies in pregnant women. It is not known whether MYOBLOC® (Botulinum Toxin Type B) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. MYOBLOC® should not be given to a pregnant woman (or nursing mother) unless it is believed that the expected benefit clearly outweighs any possible harm to the fetus (or child) or woman. (See TOXICOLOGY for Development and Reproductive Toxicity studies in animals.)

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. MYOBLOC® should not be given to a pregnant woman (or nursing mother) unless it is believed that the expected benefit clearly outweighs any possible

harm to the fetus (or child) or woman. (See TOXICOLOGY for Development and Reproductive Toxicity studies in animals.)

ANTIBODY DEVELOPMENT

Administration of any foreign protein has the potential to produce an antigenic effect. However, the clinical significance of antibodies directed against botulinum toxins is unknown. In theory, neutralizing antibodies may diminish biologic effect, however, the incidence in controlled prospective clinical trials is unknown.

PEDIATRIC USE

Safety and effectiveness in pediatric patients have not been established. There are no adequate and well-controlled studies of MYOBLOC® in pediatric patients. MYOBLOC® is not indicated in these patients. However, doses in the range of 2500 – 10,000 U used in children within or outside clinical trials have resulted in clinically significant systemic toxicity.

GERIATRIC USE

In the controlled studies, summarized in the **CLINICAL STUDIES** section, 152 (74.5%) of MYOBLOC®-treated patients 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.

SURGICAL OR OTHER STRESS

Additional precautions may be needed when higher doses of MYOBLOC® are used in patients subjected to surgical or other stress. (See TOXICOLOGY section, Study SBL 47-44)

ADVERSE REACTIONS

OVERVIEW

The most commonly reported adverse events associated with MYOBLOC® (Botulinum Toxin Type B) 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 1.

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. 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 1 reflect those adverse events occurring in at least 5% of patients exposed to MYOBLOC® treatment in pooled placebo-controlled clinical trials. 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 1: Treatment-Emergent Adverse Events Reported by at Least 5% of MYOBLOC® Treated Patients by Dose Group, Following Single Treatment Session in Controlled Studies -009, -301 and -302 Dosing Groups

Adverse Event (COSTART Term)	Dosing Groups			
	Placebo (N=104)	2500 Units (N=31)	5000 Units (N=61)	10, 000 Units (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 CD[a]	17 (16%)	0 (0%)[b]	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 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%)

a Not a COSTART term
b 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, none of these requiring medical intervention. 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.

A subsequent repeat-dose, open-label study in cervical dystonia was initiated following the U.S. approval of MYOBLOC®. Patients enrolled in this study were required to never have received Botulinum Toxin Type B and to not have had an injection of Botulinum Toxin Type A in the 12 weeks preceding enrollment. Data is available on approximately 431 patients who had received 1-3 doses of MYOBLOC® starting at 2500 to 5000 U.

The most frequently occurring adverse events were dry mouth (46%) and dysphagia (26%). Only 5% reported a serious adverse event although none were considered related to MYOBLOC®. There is no evidence that the frequency of adverse events increases with repeated usage or with increased doses of MYOBLOC®. In addition, results from clinical laboratory tests and vital signs are similar throughout the study. Based on an overall evaluation of this post-marketing data, the safety profile of MYOBLOC® remains unchanged.

Other Post-Marketing Adverse Reactions

Doses of up to 15,000 U have infrequently resulted in clinically significant systemic toxicity in adults. In the available post-marketing data, there were four reports of allergic reaction with two deemed serious. There were 96 reports of dry mouth. Six were deemed serious with three requiring hospitalization. One required insertion of a nasogastric tube. The other three were deemed medically significant with two resulting in disability. There were also 82 reports of dysphagia of which 21 were deemed serious.

IMMUNOGENICITY

In the repeat dosing open-label Phase 3 study, serum neutralizing activity was primarily not seen in patients until after 6 months. Estimated rates of development were 10% at one year and 18% percent at 18 months in the overall group of patients. 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.

In the subsequent repeat-dose, open-label study initiated following the U.S. approval of MYOBLOC®, immunogencity data is available for 345 subjects. Of these subjects, there were five with a positive antibody response to Botulinum Toxin Type B. Of these, three (<1%) became positive on their third MYOBLOC® treatment session at approximately 9 months, and two (<1%) became positive on their fourth MYOBLOC® treatment session at approximately 12 months.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Cases of overdose (some with signs of systemic toxicity) have been reported.

Symptoms of overdose are likely not to present immediately following injection(s).

Should a patient ingest the product or be accidentally overdosed, they should be monitored for up to several weeks for signs and symptoms of systemic weakness or paralysis.

In the event of an overdose, general medical supportive measures should be instituted

and an antitoxin may be administered. The antitoxin will not reverse any Botulinum Toxin induced muscle weakness effects that are already apparent. Contact ElanPharmaceuticals at 1-888-638-7605 for additional information.

DOSAGE AND ADMINISTRATION

MYOBLOC® (Botulinum Toxin Type B) should be administered intramuscularly by a physician experienced in the assessment and management of patients with cervical dystonia and the use of botulinum toxin preparations. Particular care should be taken to avoid the injection into a blood vessel.

In clinical trials to establish the safety and efficacy of MYOBLOC®, doses ranged from 5,000 to 15,000 Units. The recommended initial dose of MYOBLOC® (Botulinum Toxin Type B) based on controlled clinical trials is 10,000 Units divided among affected muscles. The dose and frequency of administration should be adjusted for each patient depending on the clinical response. The initial starting dose of 10,000 Units (or 5,000 Units) is relevant only to MYOBLOC® (Botulinum Toxin Type B). These dosage units are specific to MYOBLOC® only and are not relevant to preparations of Botulinum Toxin Type A. Patients previously on Botulinum Toxin Type A should be initiated on MYOBLOC® at a dose of 10,000 Units (or 5,000 Units)

An initial dose of 5,000 Units should be considered for patients of low body mass index (BMI).

Because Botulinum Toxin Type B and other Botulinum toxins are distinct products, dosage unit comparisons are inappropriate when considering patient treatment in order to avoid under or overdosing.

The duration of effect in patients responding to MYOBLOC® treatment has been

observed in studies to be at least 12 weeks at a dose of 10,000 Units. (See **CLINICAL STUDIES**.)

It is generally recommended that injections be no more frequent than once every 3 months, and to use the lowest effective dose for individual patient needs. As such, up to 4 treatment sessions might be expected in one year.

Treatment of Cervical Dystonia (CD) is individualized to specific patient needs depending upon the pattern and severity of dystonia. Treatment of CD with botulinum toxin should be performed by a clinician experienced in selecting and localizing target muscles for injection. Clinical trials have used 5,000-10,000 of MYOBLOC® divided over 4-6 muscles depending upon patient needs. Target muscles in the clinical trials included the sternocleidomastoid, the levator scapulae, the semispinalis capitus, the trapezius and the scalenes. In the phase 3 studies, 19% had 2 muscles injected, 48% had 3 muscles injected and 33% had 4 muscles injected. In some cases, additional cervical muscles are appropriate targets for injection, however, the total patient dose for new patients should remain in the 5,000-10,000 unit range. The total dose is divided among the target muscles based on muscle bulk, power of contraction and contribution to dystonic posture.

Lack of Response:

There are several potential explanations for a lack or diminished response to an individual treatment with MYOBLOC®. These may include inadequate dose selection, selection of inappropriate muscles for injection, muscles inaccessible to injection, underlying structural abnormalities such as muscle contractures or bone disorders,

change in pattern of muscle involvement, patient perception of benefit compared with initial results, inappropriate storage as well as neutralizing antibodies to Botulinum Toxin. A neutralizing antibody is defined as an antibody that inactivates the biological activity of the toxin.

A suggested course of action when patients do not respond to MYOBLOC® injection is: 1) wait the usual treatment interval; 2) consider reasons for lack of response listed above; 3) more than one treatment course should be considered before classification of a patient as a non-responder; 4) test patient serum for neutralizing antibody presence.

PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Common Name: Botulinum Toxin Type B

Chemical Name: Not applicable.

Structural Formula: Not applicable.

Molecular Formula: Not applicable.

Molecular Weight: Not applicable.

Description: MYOBLOC® (Botulinum Toxin Type B) Injectable Solution 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 is present in its native form as a complex of toxin and non-toxin protein with a molecular weight of approximately 700 kD. The neurotoxin complex is recovered from the fermentation process and purified through a series of precipitation and chromatography steps (3).

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 precludes extrapolation of animal dose-activity relationships to human dose estimates. The specific activity of MYOBLOC® ranges between 75 to 125

Units/ng.

COMPOSITION

MYOBLOC® is a clear and colorless to light yellow sterile solution of Botulinum Toxin Type B. Formulated MYOBLOC® contains 5000 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.

STABILITY AND STORAGE RECOMMENDATIONS

Store under refrigeration at 2-8C (36-46F). Do not use past expiry date on the label.

DO NOT FREEZE. DO NOT SHAKE.

Single use vial. (Vials are to be discarded after use.)

DILUTION

MYOBLOC® may be diluted with Sodium Chloride Injection; it should be used immediately (within 3 hours) as it does not contain a preservative. MYOBLOC® is provided at a concentration of 5,000 Units per milliliter. The recommended initial dose of MYOBLOC® is 10,000 Units divided among affected muscles. Subsequent dosing should be optimized according to the patient's individual response. MYOBLOC® was shown to be safe and well-tolerated at up to 15,000 Units per dosing session.

AVAILABILITY OF DOSAGE FORMS

MYOBLOC® (Botulinum Toxin Type B) is available in the following three presentations.

Dosage Strength	Volume Per Vial
2,500 Units	0.5 mL
5,000 Units	1.0 mL
10,000 Units	2.0 mL

Each vial is labeled and placed into a single vial carton. The single vial cartons of MYOBLOC® may be shrink-wrapped individually and in multiples of 4 and 10 for each vial presentation.

PHARMACOLOGY

CYNOMOLGUS MONKEY STUDIES

PHARMACOLOGY

The two pharmacology studies in cynomolgus monkeys used electrophysiologic endpoints to assess muscle paralysis after IM injections. In the first study (92031), the abductor pollicis brevis (APB) muscle was injected with varying doses of Botulinum Toxin Type B, ranging from 0.75 to 24 Units/kg body weight/muscle, or Botulinum Toxin Type A (BTX-A), ranging from 1.5 to 3.0 Units/kg body weight/muscle. There were 7 dose groups of 1 animal per dose group. Evoked compound muscle action potential (CMAP) were performed at various times from pre-treatment up to 16 weeks post-treatment. In this study, using the mouse unit IP LD_{50} value as the measure of comparison it appeared that a higher dose (number of units) of Botulinum Toxin Type B was required to obtain a similar duration of action as BTX-A. The paralytic effects of Botulinum Toxin Type B were maintained up to the final measurement at 16 weeks, with the high dose of 24 Units/kg/muscle resulting in 76% paralysis at that time point.

In the second study (FRC 189), the dose-response of Botulinum Toxin Type B was compared to that of BTX-A. The CMAP were measured 4 weeks post-dose in 3 females per dose group. The doses (as measured in Units) of Botulinum Toxin Type B and

BTX-A to obtain 80% paralysis were estimated using linear regression and were found to be 4.84 and 0.53 Units/muscle, respectively. This indicated that, for the APB muscle, the ratio of potency of Botulinum Toxin Type B:BTX-A was 9.1 whereas on a per nanogram basis the ratio was 0.23.

In summary, the animal pharmacology studies support a dose-related, time-dependent paralysis of skeletal muscle. At the doses used in these studies (within the pharmacological range), effects were limited to the muscle injected. In the monkey model, Botulinum Toxin Type B appeared to be less potent than BTX-A on a mouse unit IP LD50 basis but more potent on a nanogram basis, due to differences in the specific activity of the two toxin serotypes (U/ng protein). Clinical studies have demonstrated that 10,000 Units of MYOBLOC® (Botulinum Toxin Type B) divided amongst affected muscles is safe and effective in the treatment of CD (see CLINICAL STUDIES below).

SAFETY PHARMACOLOGY

Two safety pharmacology studies were performed, evaluating the effects of MYOBLOC® on blood pressure, heart rate, electrocardiogram, respiratory rate, blood gas analysis, body temperature, motor activity and behavior in conscious cynomolgus monkeys using a telemetry system. (Elan study 315-018-01 and Elan study 315-039-01). In both studies, baseline measurements were performed for a week priori to dosing, and dosing was performed as an intramuscular injection into the gluteus maximus and biceps femoris muscles.

At doses of 480 and 960 U/kg, while there was evidence of pharmacologic activity of the drug at both doses, there was no effect on cardiovascular or respiratory function,

changes in body temperature associated with drug administration, nor signs of systemic toxicity (botulism). At a dose of 1440 U/kg, however, in a study of similar design, 4 of the 6 animals died and the two remaining monkeys showed signs of systemic toxicity, evident as generalized muscle weakness and decrease in spontaneous activity. The results were unexpected and inconsistent with five other acute toxicology studies in cynomolgus monkeys where a dose 1440 U/kg, representing 10-20 times the recommended initial dose (5000 to 10,000 U), was well tolerated by the monkeys. Several factors were unique to these two safety pharmacology studies, including surgical stress, source of the monkeys, and possibly study methodologies. However, the toxicity observed in that single study at 1440 U/kg remains unexplained, in the face of toxicology studies performed both before and after this study. (Please see the **TOXICOLOGY** section of this monograph for a more complete discussion of these toxicology studies and their results.)

CLINICAL STUDIES

Two pivotal and two supportive studies established that Botulinum Toxin Type B at up to 10,000 Units per dosing session is safe and efficacious in the management of patients with cervical dystonia (CD) who are either Botulinum Type A toxin responsive or Toxin Type A resistant (secondary non-responders). These studies suggest that patients who demonstrate a clinically significant response at Week 4 can anticipate the duration of treatment effect to be approximately 12 weeks at a dose of 10,000 U and possibly shorter following lower doses.

The two pivotal studies were designed as randomized, multi-center, double-blind, placebo-controlled trials. The first pivotal study (Study -301) enrolled only patients responsive to Botulinum Type A toxin, while the other pivotal study (Study -302) enrolled only Type A toxin resistant patients.

The primary efficacy outcome variable in each study was the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-Total Score (5) (range 0-87) at Week 4. The supportive secondary variable was the Patient Global Assessment at Week 4. Results of comparisons of the primary and secondary efficacy variables between the 10,000 Units and placebo groups for each of the pivotal studies are summarized in Table 2.

Table 2 - Efficacy Results From Two Phase 3 MYOBLOC® Studies

Assessments*	STUDY 301 Placebo	STUDY 301 5000 U	STUDY 301 10000 U	STUDY 302 Placebo	STUDY 302 10000 U
	n = 36	n = 36	n = 37	n = 38	n = 39
TWSTRS Total					
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)
p value		0.012	0.0004		0.0001
Patient Global					
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)
p value		0.001	0.0001		0.0001
Physician Global					
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)
p value		0.001	0.004		0.0001
TWSTRS – Subscales					
– Severity					
Mean at Baseline	18.4	20.2	20.2	22.1	22.6
Mean at Week Four	16.2	17.0	15.4	21.0	18.9
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)
p value		0.22	0.002		0.001
– Pain					
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)
p value		0.002	0.0008		0.0001
– Disability					
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)
p 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-subscales 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.

In Study -301, patients received IM injections of Botulinum Toxin Type B (5,000 or 10,000 Units) or placebo into two to four affected neck and/or shoulder muscles at a single dosing session. Evaluations occurred for a maximum of 16 weeks post-treatment. Of 109 patients enrolled, 36 received placebo, 36 received 5,000 Units Botulinum Toxin Type B, and 37 received 10,000 Units Botulinum Toxin Type B. The groups were well balanced for demographics and baseline characteristics. Statistically significant improvements were demonstrated in patients receiving either 5,000 Units or 10,000 Units as compared to those receiving placebo alone. Data from clinical trials suggest that efficacy is dose dependent but these trials, because they were not powered for comparison, do not show a significant difference between the two active groups. Mean improvements on the TWSTRS-Total Score at baseline to Week 4 (Table 2) for the 10,000 Units versus placebo groups were 11.7 and 4.3, respectively (p-value = 0.0004). Mean values on the Patient Global Assessment at Week 4 for the 10,000 Units versus placebo groups were 64.6 and 43.6, respectively, on a 100-mm scale (p-value = 0.0001). Mean improvements on the TWSTRS-Total Score at baseline to Week 4 for the 5,000 Units versus placebo groups were 9.3 and 4.3, respectively (p-value = 0.0115). Mean values on the Patient Global Assessment at Week 4 for the 5,000 Units versus placebo groups were 60.6 and 43.6, respectively, on a 100-mm scale (p-value = 0.0010).

In Study -302, patients received IM injections of Botulinum Toxin Type B (10,000 Units) or placebo divided among two to four affected neck and/or shoulder muscles at a single dosing session. Evaluations occurred for a maximum of 16 weeks post-treatment. Of 77 patients enrolled, 38 received placebo and 39 received 10,000 Units Botulinum Toxin

Type B. The groups were well balanced for demographics and baseline characteristics. Statistically significant improvements were demonstrated in patients receiving 10,000 Units versus placebo. Mean improvements on the TWSTRS-Total Score at baseline to Week 4 (Table 2) for the 10,000 Units versus placebo groups were 11.1 and 2.0, respectively (p-value = 0.0001). Mean values on the Patient Global Assessment at Week 4 for the 10,000 Units versus placebo groups were 60.2 and 39.5, respectively, on a 100-mm scale (p-value = 0.0001).

The data from two supportive controlled studies (Studies -008 and -009) demonstrated similar findings. These were randomized, double-blind, placebo-controlled studies, which enrolled a combined total of 207 adults with CD. These supportive studies demonstrated a dose-response when assessing doses of Botulinum Toxin Type B over the range of 400 to 10,000 Units per dosing session. On average, greater improvement was noted with increasing dose per dosing session as measured on the TWSTRS-Total score, baseline to Week 4.

TOXICOLOGY

Botulinum Toxin Type B is used as an IM injection to result in local paralytic activity. Small (nanogram) quantities of this protein drug are administered and no systemic exposure is expected at tolerated doses. Therefore, no carcinogenicity, or mutagenicity studies were performed.

Several acute toxicity studies were performed in cynomolgus monkeys, some including electrophysiological measurements, and one repeated dose study has been completed in cynomolgus monkeys, with additional repeated dose studies in nonprimate species

(rats and rabbits) being performed as part of developmental and reproductive toxicity.

ACUTE TOXICITY

Four nonclinical studies were performed that included both standard toxicological endpoints and electrophysiologic measurements. In these studies, the monkeys were given a number of IM injections of Botulinum Toxin Type B with total doses ranging from 1.5 to 2400 Units/kg and the degrees of paralysis of the injected muscles were measured by electromyography. The untreated muscles contralateral to the injected muscles were also measured to assess systematic effects after the local injection. In addition, nerve conduction velocity and somatosensory evoked potentials were performed to assess afferent and efferent nerve function.

The portions of these studies conducted at the higher doses, as well as the results of an additional (toxicology only) study were performed to determine the maximum tolerated dose (MTD) of Botulinum Toxin Type B. The monkeys were observed for clinical signs that would be expected from Botulinum Toxin poisoning, and body weights and food consumption were measured. The results of these studies indicated that at toxic doses, the same general signs of systemic toxicity observed from clinical reports of human botulism were found. As noted in Table 3 below, in these studies, all 10 animals given doses of between 1400 and 1500 U/kg survived, and only 1 of 10 demonstrated signs of systemic toxicity. These results are in direct contrast to the results of the safety pharmacology study conducted at 1440 U/kg as described above.

Table 3: Summary of Results from Toxicology Studies

Elan Number	Site Number	Animal Number	Weight (kg)	MYOBLOC Dose (U/kg)	Total Dose (U/monkey)	Outcome
315-039-01	SBL 47-45	2M	3.9	480	1882	No effect
315-039-01	SBL 47-45	3M	4.1	480	1987	No effect
315-039-01	SBL 47-45	4F	4.0	480	1925	Reversible forelimb paralysis
NA	FRC 580	DXL17-43 M	3.3	720	2376	No effect
NA	FRC 580	DXM2-40Q F	3.6	720	2592	No effect
NA	FRC 580	DXC7-29Q F	3.2	960	3072	No effect
NA	FRC 580	LXL2-48Q M	4.3	960	4128	No effect
NA	FRC 804	301 M	3.4	960	3264	No effect
NA	FRC 804	351 F	3.8	960	3648	No effect
315-039-01	SBL 47-45	1M	3.9	960	3734	No effect
315-039-01	SBL 47-45	5F	3.9	960	3763	No effect
315-039-01	SBL 47-45	6F	3.7	960	3552	No effect
315-002-02	SBI 1314-93	2-FN18340F	2.4	1417	3401	No effect
315-002-02	SBI 1314-93	2-FN19504M	2.4	1417	3401	No effect
NA	FRC 580	DXC7-2Q F	3.3	1440	4752	No effect
NA	FRC 580	LXC3-9Q M	4.4	1440	6336	No effect
NA	FRC 804	101 M	4.2	1440	6048	Reversible systemic weakness
NA	FRC 804	151 F	3.2	1440	4608	No effect
315-018-01	SBL47-44	1 M	4.7	1440	6696	Died
315-018-01	SBL47-44	2 M	4.6	1440	6653	Died
315-018-01	SBL 47-44	3 M	4.9	1440	7027	Reversible systemic weakness involving respiratory function
315-018-01	SBL 47-44	4 F	3.5	1440	5040	Died
315-018-01	SBL 47-44	5 F	3.7	1440	5299	Died
315-018-01	SBL 47-44	6 F	4.3	1440	6120	Reversible systemic weakness involving respiratory function
315-002-02	SBI 1314-93	2-FN19710M	2.2	1455	3201	No effect
315-002-02	SBI 1314-93	2-FN18865F	2.3	1478	3399	No effect
315-002-02	SBI 1314-93	2-FN190100F	2.1	1905	4001	No effect
NA	FRC 580	DXL17-32 M	3.6	1920	6912	Reversible systemic weakness involving respiratory function
NA	FRC 580	LXC3-1Q M	4.3	1920	8256	Reversible systemic weakness involving respiratory function

Elan Number	Site Number	Animal Number	Weight (kg)	MYOBLOC Dose (U/kg)	Total Dose (U/monkey)	Outcome
NA	FRC 580	LXC3-58Q F	3.3	1920	6336	Reversible systemic weakness
315-002-02	SBI 1314-93	2-FN19503M	2.7	1926	5200	Reversible systemic weakness
NA	FRC 804	201 M	6.4	1990	12736	Reversible systemic weakness
NA	FRC 804	251 F	3.1	1990	6169	No effect
NA	FRC 580	DXC7-28Q F	3.9	2400	9360	Irrversible systemic weakness. Sacrificed moribund

In summary, single dose intramuscular toxicology studies have been performed in cynomolgus monkeys. The systemic No Observed Effect Level (NOEL) was shown to be approximately 960 U/kg. The dose consistently resulting in death was 2400 U/kg, with deaths observed in a single anomalous study at 1440 U/kg. In this study (SBL 47-44), the results were unexpected and inconsistent with other studies in cynomolgus monkeys were a dose of 1440 U/kg, representing 10-20 times the recommended inital dose (5000 to 10,000 U), was well tolerated by the monkeys. Surgical stress (telemetry device implantation), the source of the monkeys and the animal size were raised as possible factors contributing to the observed serious toxicity in SBL 47-44. Special care may be appropriate when using higher doses under similar conditions, in the clinical setting.

The maximum doses that resulted in no systemic effects were shown to be 600- and 30-fold the doses required to result in 80% paralysis in the APB and trapezius muscles, respectively (on a Units/kg basis). The effects on both local and distant muscle paralysis, at nonlethal doses, are reversible. The electrophysiologic studies did not

indicate the spread of the paralytic effects of Botulinum Toxin Type B to contralateral muscles at the doses tested within the pharmacological range. At high doses, electrophysiologic evidence of denervation was observed in neighboring non-injected muscles. Electrophysiologic measurements to assess nerve conduction velocity and somatosensory evoked potentials did not reveal other peripheral or central neurotoxicity. There were no signs of organ toxicity. Thus, the toxicology of Botulinum Toxin Type B appears to be restricted to an extension of its pharmacological effect of paralysis of skeletal muscle.

Definitive toxicity studies evaluating the effects of combined treatment with Botulinum Toxin Types A and B have not been performed in nonhuman primates. An efficacy study evaluating the effects of Botulinum Toxin Types B and A (co-administered) after intramuscular injection into the gastrocnemius muscle of nonhuman primates is in progress. This study was designed to establish the maximum paralytic effect of the two serotypes and to compare the duration of the induced effects at doses expected to have comparable initial paralytic efficacy. In this study, cynomolgus monkeys were co-administered Botulinum Toxin Type B and Botulinum Toxin Type A into contra-lateral muscles at the following dose levels, respectively (100 U/kg and 1.6 U/kg, 200 U/kg and 3.2 U/kg, 400 U/kg and 6.4 U/kg or 800 U/kg and 12.8 U/kg). One animal in the high dose group (800 U/kg Botulinum Toxin Type B and 12.8 U/kg Botulinum Toxin Type A) exhibited nonreversible systemic toxicity. Reversible systemic toxicity was observed in the remaining animals in this group. The results of this efficacy study showed that co-administration of the two serotypes, particularly at higher doses, is not recommended in the absence of better safety information.

REPEATED DOSE TOXICITY

In a single study in which the effects of repeated dose toxicity was evaluated, one dose group was administered a dose of 120 U/kg as part of a pharmacology/ safety study in which EMG analysis of injected and uninjected muscles were performed, along with measurement of somatosensory evoked potentials, ophthalmology, and ECG. 4 weeks later, a second dose of 480 U/kg was administered. In another dose group, animals received a dose of 240 U/kg, followed 12 weeks later by 240 U/kg. Neither dosing regimen appeared to be associated with systemic toxicity.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY

Development studies (Segment II) in female rats and rabbits and a fertility study (Segment I) in rats, have been conducted with MYOBLOC® (Botulinum Toxin Type B). The results show important species-specific differences in levels causing toxicity. There was no evidence of fetal malformations or developmental anomalies and no significant changes in fertility parameters at the tested doses. In the development studies, the No Observed Adverse Effect Dose Level (NOAEL) in rats was determined to be 1000 U/kg/day for maternal effects and 3000 U/kg/day for fetal effects. In rabbits, the NOAEL was 0.1 U/kg/day for maternal effects and 0.3 U/kg/day for fetal effects. In the fertility study in rats, the NOAEL was 300 U/kg/day for general toxicity in males and females and 1000 U/kg/day for fertility and reproductive performance.

SELECTED BIBLIOGRAPHY

1. Schiavo G, Benfenati F, Poulain B, et al. Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin. Nature. 1992; 359: 832-5.
2. Blasi J, Chapman ER, Link E, et al. Botulinum neurotoxin A selectively cleaves the synaptic protein SNAP-25. Nature 1993; 365: 160-3.
3. Settler P. The Biochemistry of botulinum toxin type B. Neurology 55 (suppl 5), S22-S28.
4. Hatheway CL, Dang C. Immunogenicity of the neurotoxins of clostridium botulinum. In: Jankovic J, Hallet M, editors. Therapy with botulinum toxin. New York, Marcel Dekker, Inc., 1994; 8: 93-107.
5. Consky ES, Lang AE. Clinical assessments of patients with cervical dystonia. In: Jankovic J, Hallet M, editors. Therapy with botulinum toxin. New York, Marcel Dekker, Inc., 1994; 8: 211-37.
6. Blackie JD, Lees AJ. Botulinum toxin treatment in spasmodic torticollis. J Neurol Neurosurg Psychiatry 1990; 53: 640-3.
7. Boghen D, Flanders M. Effectiveness of botulinum toxin in the treatment of spasmodic torticollis.Eur Neurol 1993; 33: 199-203.
8. Burgen ASV, Dickens F, Zatman LJ. The action of botulinum toxin on the neuro-muscular junction. J Physiol 1949; 109: 10-24.
9. Conference Report, Clinical use of botulinum toxin. National Institutes of Health Consensus Development Conference Statement. Arch Neurol 1991; 48: 1294-8.

10. Gauthier S. Idiopathic spasmodic torticollis: pathophysiology and treatment. Can J Neurol Sci 1986; 13(2): 88-90.

11. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. N Engl J Med 1991; 324: 1186-94.

12. Jankovic J, Leder S, Warner D, Schwartz K. Cervical dystonia: clinical findings and associated movement disorders. Neurol 1991; 41: 1088-91.

13. Jankovic J, Schwartz KS. Clinical correlates of response to botulinum toxin injections. Arch Neurol 1991; 48: 1253-56.

14. Lew MF, Adornato BT, Duane DD, Dykstra DD, Factor SA, Massey JM. Botulinum toxin type B: A double-blind, placebo-controlled, safety and efficacy study in cervical dystonia. Neurol 1997; 9: 701-7.

15. Montecucco C, Schiavo G. Tetanus and botulism neurotoxins: a new group of zinc proteases. TIBS 1993; 18: 324-7.

16. Sugiyama H. Clostridium botulinum neurotoxin. Microbiol Rev 1980; 44; 419-48.

17. Tsui JKC, Eisen A, Calne DB. Botulinum toxin in spasmodic torticollis. Adv Neurol 1988; 50: 593-7

18. Tsui JKC, Eisen A, Stoessl AJ, Calne S, Calne DB. Double-blind study of botulinum toxin in spasmodic torticollis. Lancet 1986; 2: 245-7.

19. Zuber M, Sebald M, Bathien N, de Recondo J, Rondot P. Botulinum antibodies in dystonic patients treated with Type A botulinum toxin: frequency and significance. Neurol 1993; 43: 1715-8.

20. Dressler D and Benecke R, Arch Pharmacol (2002; 365; suppl 2, R17)

21. Dressler D and Benecke R, Nervenarzt (2002; 73(2):194-8)