MYOBLOC™
Botulinum Toxin Type B
Injectable Solution

Elan Pharmaceuticals, Inc.
U.S. License No. 1579

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 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 5000 U 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 Elan Pharmaceutical's 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 70 to 130 U/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

Though pharmacokinetic or ADME studies were not performed, MYOBLOC™ is not expected to be present in the peripheral blood at measurable levels following IM injection at the recommended doses. The recommended quantities of neurotoxin administered at each dosing session are not expected to result in systemic, distant overt clinical effects in patients without other neuromuscular dysfunction. While MYOBLOC has not been assessed for systemic effects, systemic effects have been shown by electromyography after IM doses of other botulinum toxins appropriate to produce clinically observable local muscle weakness.

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, 5000U or 10000 U of MYOBLOC™, and subjects in Study #302 were randomized to receive placebo or 10000 U 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 capitus, Sternocleidomastoid, Levator scapulae, Trapezius, Semispinalis capitus, 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 a patient to indicate how they feel at the time of the evaluation compared to the pre-injection baseline. Likewise, the Physician Global indicates the physician's assessment of the 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	5000 U	10000 U	Placebo	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
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-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 5000 U and 10000 U 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, that 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 U, 1200 U, or 2400 U (21 or 22 subjects per group). Study #09 enrolled 122 subjects and randomized between doses of placebo, 2500 U, 5000 U, and 10000 U (30 or 31 subjects per group). These studies demonstrated efficacy on the TWSTRS-Total, baseline to Week 4, at doses of 2400 U, 2500 U, 5000 U, and 10,000 U. Study #08 showed mean improvement from baseline on the Week 4 TWSTRS for placebo and 2400 U 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, 2500 U, 5000 U, and 10,000 U 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 2400 U.

Study #352 was an open label, intrapatient dose-escalation study of 3 treatment sessions where each patient with cervical dystonia sequentially received 10000 U, 12500 U, and 15000 U, 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 Capitus	88	0.30	0.40	0.50
Sternocleidomastoid	80	0.20	0.25	0.30
Semispinalis Capitus	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 patients 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 ingredient in the formulation.

WARNINGS

Do not exceed the doses of MYOBLOC™, described under Dosage and Administration. Risks resulting from administration at higher doses are not known.

Caution should be exercised when administering MYOBLOC to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of MYOBLOC™. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses. In some cases, dysphagia has lasted months and required placement of a gastric feeding tube.

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.

Dysphagia is a commonly reported adverse event following treatment with all botulinum toxins in cervical dystonia patients. In the medical literature, there are reports of rare cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There are also rare case reports where subsequent to the finding of dysphagia a patient developed aspiration pneumonia and died.

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).

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 12500 U or less. There were 57 patients administered a dose of 20000 or 25000 U. 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

	Dosing Groups			
Adverse Event (COSTART Term)	Placebo (N=104)	2500 U (N=31)	5000 U (N=67)	10,000 U (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.

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

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 an antitoxin may be adminstered. Contact Elan Pharmaceuticals at 1-888-638-7605 for additional information and your State Health Department to process a request for antitoxin through the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. The antitoxin will not reverse any botulinum toxin induced muscle weakness effects already apparent by the time of antitoxin administration.

DOSAGE AND ADMINISTRATION

The recommended initial dose of MYOBLOC™ for patients with a prior history of tolerating botulinum toxin injections is 2500 to 5000 U 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 Elan Pharmaceutical's 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 5000 U or 10,000 U (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 5000 U[a] 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.

[a] See Dosage and Administration.

MYOBLOC™ is available in the following three presentations.

Dosage Strength	Volume Per Vial	Single-Vial Carton
2500 U	0.5 mL	NDC 59075-710-10
5000 U	1.0 mL	NDC 59075-711-10
10,000 U	2.0 mL	NDC 59075-712-10

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

DO NOT FREEZE. DO NOT SHAKE.

The recommended storage condition for MYOBLOC™ is refrigeration at 2-8°C for up to 21 months.

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.

Single use vial.

Rx Only

Manufactured By:

Elan Pharmaceuticals, Inc., South San Francisco, CA 94080

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