CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA 103000/5189

Trade Name: Botox Injection

Generic Name: onabotulinumtoxinA

Sponsor: Allergan, Inc.

Approval Date: March 9, 2010

Indications: For the treatment of upper limb spasticity in adult patients; cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain; severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients; blepharospasm associated with dystonia in patients ≥ 12 years of age; and strabismus in patients ≥ 12 years of age.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

APPROVAL

Our STN: BLA STN [103000/5189]

Allergan, Inc.
Attention: Gus Aromin
Director, Global Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612-1599

Dear Mr. Aromin:

Please refer to your supplement to your biologics license application (BLA), dated September 29, 2009, received September 30, 2009 submitted under section 351 of the Public Health Service Act for Botox (onabotulinumtoxinA) Injection.

We also acknowledge receipt of your amendments dated November 13, November 24, December 28, 2009; and your REMS assessment dated January 14, 2010.

Your submission of September 29, 2009 constituted a complete response to our May 22, 2009, action letter.

This supplement to your BLA provides for the use of Botox (onabotulinumtoxinA) Injection for the treatment of upper limb spasticity and proposes modifications to the Medication Guide and the approved Risk Evaluation and Mitigation Strategy (REMS).

Your request to supplement your biologics license application for Botox (onabotulinumtoxinA) has been approved.

CONTENT OF LABELING

Within 14 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm that is identical in content to the enclosed labeling text. The content of labeling should be submitted by updating your applications by referencing the SPL file submitted to the drug establishment registration and drug listing system. To do this, place a link in your application submissions that directs FDA to your SPL file. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 103000/5189.**" In addition,

within 14 days of the date of this letter, amend any pending supplements for this BLA with content of labeling in SPL format to include the changes approved in this supplement. For additional information on submitting labeling to drug establishment registration and drug listing and to applications, see the FDA guidances at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

We request that the revised labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth through 23 months of age because the necessary studies are impossible or highly impracticable. Spastic cerebral palsy, the main cause of spasticity in that age group, is not reliably diagnosed until after two years of age; therefore, there is a limited population of patients and the patients are geographically dispersed.

We are deferring submission of pediatric studies for ages 2 through 16 years 11 months for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 601.70 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

PMR – 1:.

A juvenile rat toxicology study under PREA to identify the unexpected serious risk of adverse effects of Botox on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study

must evaluate effects of Botox on growth, reproductive development, and neurological and neurobehavioral development.

Final Protocol submission:	March 31, 2010
Study Completion:	February 28, 2011
Final Report Submission:	December 31, 2011

PMR-2:

Deferred pediatric efficacy study under PREA for the treatment of upper limb spasticity, to decrease the severity of increased muscle tone in the elbow flexors, wrist flexors and finger flexors in pediatric patients ages 2 years through 16 years 11 months.

Final Protocol submission:	June 30, 2010
Study Completion:	May 31, 2015
Final Report Submission:	January 15, 2016.

PMR-3:

Deferred pediatric long-term safety study (minimum 12 months) under PREA for the treatment of upper limb spasticity in pediatric patients ages 2 years through 16 years 11 months. The doses evaluated must be at least as high as those shown effective in the pediatric efficacy study (PMR-2), or those commonly used to treat upper limb spasticity in pediatric patients, if an effective dose is not identified in the pediatric efficacy study (PMR-2). The study must assess distant spread of toxin effects, and the effects of Botox on blood glucose and alkaline phosphatase. The study report must include safety information on at least 300 patients who received 2 injections over a 6-month period, with at least 100 patients who received the highest recommended dose (if any), and safety information on at least 100 patients who received 4 injections over a 12-month period, with at least 60 patients who received the highest recommended dose (if any).

Final Protocol submission:	June 30, 2010
Study Completion:	May 31, 2015
Final Report Submission:	January 15, 2016.

Submit final study reports to this BLA. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated **"Required Pediatric Assessment".**

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Botox (onabotulinumtoxinA) Injection was originally approved on July 31, 2009. The proposed REMS modification, submitted on December 28, 2009, contains a revised Medication Guide reflecting the addition of upper limb spasticity as an indication.

Your proposed modified REMS, appended to this letter, is approved. The REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS. The timetable for submission of assessment will remain the same as that approved on July 31, 2009.

There are no changes to the REMS assessment plan described in our July 31, 2009 letter.

Prominently identify submissions containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

BLA 103000 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 103000
PROPOSED REMS MODIFICATION
REMS ASSESSMENT

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 103000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

If you have any questions, call Vandna Kishore, R.Ph., Regulatory Project Manager, at (301) 796-4193.

Sincerely,

/ Russell Katz/

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures: Appendix A: REMS
Package Insert/Medguide

CENTER FOR DRUG EVALUATION AND RESEARCH

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OTHER ACTION LETTERS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

COMPLETE RESPONSE

Our STN: BL 103000/5189

Allergan, Inc.
ATTENTION: Michele LaRussa-Goepel
Director, Global Regulatory Liaison
2525 Dupont Drive; P.O. Box 19534
Irvine, California 92623-9534

COMPLETED MAY 2 2 2009

Dear Ms. LaRussa-Goepel:

Please refer to the supplement to your biologics license application, dated August 20, 2008, received August 22, 2008, submitted under section 351 of the Public Health Service Act for Botox (botulinum toxin type A) Neurotoxin Complex.

This supplement proposes the use of Botox Neurotoxin Complex in the treatment of upper limb spasticity in post-stroke adult patients.

We acknowledge receipt of your additional amendments dated November 6, 2008, December 5, 2008 and February 20, 2009. We also acknowledge receipt of your amendment dated May 18, 2009, which was not reviewed for this action.

We have completed the review of your supplement, as amended, and have determined that we cannot approve this supplement in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

RISK MANAGEMENT AND MITIGATION STRATEGY

We refer to our April 29, 2009 letter, requiring safety labeling changes under section 505(o)(4) of the Food, Drug, and Cosmetic Act (FDCA) and a Risk Evaluation and Mitigation Strategy (REMS) under section 505-1 of the FDCA. We note that your May 18, 2009 amendment contained a response to our April 29, 2009 letter which, as noted above, was not reviewed for this action. Your supplement 5189 cannot be approved without an approved REMS in place. You must incorporate applicable sections of the proposed REMS by specific reference as part of your response to the deficiencies cited in this letter. The REMS, once approved, will create enforceable obligations.

SOURCE DATA DOCUMENTATION

Although we acknowledge that, on face, your supplement supports the efficacy and safety of Botox for the treatment of upper limb spasticity, the inspection of study sites of the two pivotal studies by the Division of Scientific Investigations, and the subsequent communications with you during the review cycle identified significant issues with source data documentation.

Specifically, the Division of Scientific Investigations could not verify the study records at one of sites of Study 191622-008 (Site 2373, from Mark Gordon, MD – New Hyde Park, NY). In addition, drug accountability records and informed consent documents could not be verified. The lack of source documents made it impossible to verify the conduct of this study site and the integrity of the data. Therefore, the data generated from this site can not be used in support of the proposed indication.

On February 13, 2009, the Division held a teleconference with you to address questions related to Study Site 2373. During that meeting, the Division requested your internal audit reports from Study 191622-008, as well as any additional relevant information pertaining to the general study conduct, and any source documentation currently available at Site 2373, as well as all other participating sites.

In your response, you noted that you contacted and/or visited all sites to confirm that source documents were available. However, you also indicated that source documentation was not available in three other sites (2329, 2512 and 3009), involving an additional 14 patients.

Even though the documentation that you provided (audit reports and clinic notes) suggests that patients were indeed enrolled and studied at these sites, the documentation is insufficient to verify the integrity of the eligibility criteria, the primary and secondary efficacy endpoints, and the occurrence of any adverse reaction in these patients. The identification of four sites with inadequate source data documentation during the review cycle questions not only the integrity of the database of Study 191622-008, but also of the other pivotal and supportive studies.

In order to address that issue, you must conduct a third party audit to verify adequate source data are available for the 12 sites not yet inspected by the Agency or identified by you as lacking adequate source data documentation. You must also provide a reanalysis of Study 191622-008, excluding the sites with missing source data documentation. Based on the results of that audit and reanalysis, the Division will decide whether a similar audit and reanalysis is necessary for other pivotal or supportive studies.

PEDIATRIC WAIVER REQUEST

You requested in your application a waiver for [redacted] (b) (4)

However, the Division believes that the proposed restriction of the proposed patient population to post-stroke spasticity is pseudo-specific, considering the focal nature of Botox treatment, and the similarities of upper limb spasticity across conditions causing it. Therefore, the indication considered by the Division is not restricted to stroke patients. As the Division believes that there is an adequate number of pediatric patients with spasticity of origins other than stroke (e.g. cerebral palsy), you must submit a revised proposed pediatric plan, to assess the safety and efficacy of Botox for the treatment of upper l spasticity in pediatric patients age 2-(b) (4). The Division believes that a waiver for patients age 0-23 months is acceptable.

LABELING

Submit draft labeling that incorporates revisions in the attached labeling. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html.

When responding to this letter, submit labeling that includes all previous revisions, as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations with the supplement number for previously-approved labeling changes.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
   - Present tabulations of the new safety data combined with the initial data.
   - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.

6. Provide updated exposure information for the clinical trials (e.g. number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

9. Provide an updated report of Study 191622-057, which was ongoing at the time of review of this Supplement.

OTHER

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings With Sponsors and Applicants for PDUFA Products,* February, 2000 (http://www.fda.gov/cder/guidance/2125fnl.htm).

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact Stacy Metz, PharmD, Regulatory Project Manager, at (301) 796-2139.

Sincerely,

Signed for Russell Katz, M.D.
Director, Division of Neurology Products
Office of Drug Evaluation I,
Center for Drug Evaluation and Research

Eric Bastings, MD
Deputy Director, Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

26 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BOTOX® safely and effectively. See full prescribing information for BOTOX.

BOTOX (onabotulinumtoxinA)
Initial U.S. Approval: 1989

WARNING: Distant Spread of Toxin Effect
See full prescribing information for complete boxed warning.
The effects of **BOTOX** and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These 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, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

RECENT MAJOR CHANGES

- Boxed Warning, Distant Spread of Toxin Effect 7/2009
- Indications and Usage, Upper Limb Spasticity (1.1) 3/2010
- Dosage and Administration, Upper Limb Spasticity (2.2) 3/2010
- Warnings and Precautions (5.1, 5.2, 5.4) 7/2009
- Warnings and Precautions (5.3, 5.6, 5.9) 3/2010

INDICATIONS AND USAGE

BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for the treatment of:

- Upper limb spasticity in adult patients (1.1)
- Cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.2)
- Severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.3)
- Blepharospasm associated with dystonia in patients ≥12 years of age (1.4)
- Strabismus in patients ≥12 years of age (1.4)

Important limitations:

- Safety and effectiveness of **BOTOX** have not been established for the treatment of upper limb spasticity in pediatric patients, and for the treatment of lower limb spasticity in adult and pediatric patients.
- Safety and effectiveness of **BOTOX** for hyperhidrosis in body areas other than axillary have not been established.

DOSAGE AND ADMINISTRATION

- Indication specific dosage and administration recommendations should be followed; Do not exceed a total dose of 360 Units (U) administered every 12 to 16 weeks or at longer intervals (2)
- See Preparation and Dilution Technique for instructions on **BOTOX** reconstitution, storage, and preparation before injection (2.1)
- Upper Limb Spasticity: Select dose based on muscles affected, severity of muscle activity, prior response to treatment, and adverse event history; Electromyographic guidance recommended (2.2)
- Cervical Dystonia: **Base dosing on the patient's head and neck** position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients (2.3)
- Axillary hyperhydrosis: 50 U per axilla (2.4)
- Blepharospasm: 1.25-2.5 U into each of 3 sites per affected eye (2.5)
- Strabismus: 1.25-2.5 U initially in any one muscle (2.6)

DOSAGE FORMS AND STRENGTHS

Single-use, sterile 50 U or 100 U vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection (3)

CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4.1, 5.3, 6.2)
- Infection at the proposed injection site (4.2)

WARNINGS AND PRECAUTIONS

- Potency Units of **BOTOX** not interchangeable with other preparations of botulinum toxin products (5.1, 11)
- Spread of toxin effects; swallowing and breathing difficulties can lead to death (5.2)
- Immediate medical attention may be required in cases of respiratory, speech or swallowing difficulties (5.2, 5.4)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.4, 5.6)
- Corneal exposure and ulceration (5.7)
- Retrobulbar hemorrhages and compromised retinal circulation (5.8)
- Bronchitis and upper respiratory tract infections in patients treated for upper limb spasticity (5.9)

ADVERSE REACTIONS

In controlled studies, the most commonly observed adverse reactions (≥ 5% and > placebo) were:

- Spasticity: pain in extremity (6.1)
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis (6.1)
- Axillary Hyperhydrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Patients receiving concomitant treatment of **BOTOX** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of **BOTOX** may be potentiated (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Pediatric Use: Safety and efficacy are not established in patients under 18 years of age for the treatment of upper limb spasticity and axillary hyperhydrosis, in patients under 16 years of age for the treatment of cervical dystonia, and in patients under 12 years of age for the treatment of blepharospam and strabismus (8.4)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: 03/2010

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- 5.6 Pulmonary Effects of **BOTOX** in Patients with Compromised Respiratory Status Treated for Spasticity
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8 USE IN SPECIFIC POPULATIONS
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17 PATIENT COUNSELING INFORMATION
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17.3 Medication Guide

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

Distant Spread of Toxin Effect

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

1 INDICATIONS AND USAGE

1.1 Upper Limb Spasticity

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor digitorum sublimis).

Important limitations

Safety and effectiveness of **BOTOX** have not been established for the treatment of other upper limb muscle groups, or for the treatment of lower limb spasticity. Safety and effectiveness of **BOTOX** have not been established for the treatment of spasticity in pediatric patients under age 18 years. **BOTOX** has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with **BOTOX** is not intended to substitute for usual standard of care rehabilitation regimens.

1.2 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.3 Primary Axillary Hyperhidrosis

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

Important limitations

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

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

1.4 Blepharospasm and Strabismus

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

2 DOSAGE AND ADMINISTRATION

The potency Units of **BOTOX** (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of **BOTOX** cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Warnings and Precautions (5.1) and Description (11)]*.

Injection specific dosage and administration recommendations should be followed. In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval.

The safe and effective use of **BOTOX** depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering **BOTOX** must understand the relevant neuromuscular and/or orbital anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures. An understanding of standard electromyographic techniques is also required for treatment of strabismus and of upper limb spasticity, and may be useful for the treatment of cervical dystonia.

Use caution when **BOTOX** treatment is used in the presence of inflammation at the proposed injection site(s) or when excessive weakness or atrophy is present in the target muscle(s).

2.1 Preparation and Dilution Technique

BOTOX is supplied in a single-use 50 Units and 100 Units vial. Prior to injection, reconstitute each vacuum-dried vial of **BOTOX** with sterile, non-preserved 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size syringe (Dilution Table), and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix **BOTOX** with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. **BOTOX** should be administered within 24 hours after reconstitution. During this time period, reconstituted **BOTOX** should be stored in a refrigerator (2° to 8°C).

Dilution Table: 0.9% Sodium Chloride Injection
Dilution Instructions for 50 Unit and 100 Unit BOTOX Vials

Diluent* Added to **50 Unit** Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to **100 Unit** Vial	Resulting Dose Units per 0.1 mL
1 mL	5 Units	1 mL	10 Units
2 mL	2.5 Units	2 mL	5 Units
4 mL	1.25 Units	4 mL	2.5 Units
		8 mL	1.25 Units

*0.9% Sodium Chloride Injection Only

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the **BOTOX** dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

An injection of **BOTOX** is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile, needle and syringe should be used to enter the vial on each occasion for removal of **BOTOX**.

Reconstituted **BOTOX** should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

2.2 Upper Limb Spasticity

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the **presence of local muscle weakness, the patient's response** to previous treatment, or adverse event history with **BOTOX**.

In clinical trials, doses ranging from 75 Units to 360 Units were divided among selected muscles at a given treatment session.

Following are recommended dose ranges per muscle:

	Total Dosage (Number of Sites)
Biceps Brachii	100 - 200 Units divided in 4 sites
Flexor Carpi Radialis	12.5 - 50 Units in 1 site
Flexor Carpi Ulnaris	12.5 - 50 Units in 1 site
Flexor Digitorum Profundus	30 - 50 Units in 1 site
Flexor Digitorum Sublimis	30 - 50 Units in 1 site

The recommended dilution is 100 Units/2 mL with 0.9% non-preserved sterile saline (see Dilution Table). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with electromyographic guidance or nerve stimulation techniques is recommended.

Repeat **BOTOX** treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of **BOTOX** and muscles to be injected.

2.3 Cervical Dystonia

The phase 3 study enrolled patients who had extended histories of receiving and tolerating **BOTOX** injections, with prior individualized adjustment of dose. The mean **BOTOX** dose administered to patients in the phase 3 study was 236 Units (25th to 75th percentile range of 198 Units to 300 Units). The **BOTOX** dose was divided among the affected muscles *[see Clinical Studies (14.2)]*. Dosing in initial and sequential treatment sessions should **be tailored to the individual patient based on the patient's** head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of **BOTOX** should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscle to 100

Units or less may decrease the occurrence of dysphagia *[see Warnings and Precautions (5.2, 5.4, 5.5)].*

The recommended dilution is 100 Units/1 mL or 100 Units/2 mL with 0.9% non-preserved sterile saline, depending on volume and number of injection sites desired to achieve treatment objectives (see Dilution Table). In general, no more than 50 Units per site should be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with electromyographic guidance may be useful.

Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the phase 3 study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

2.4 Primary Axillary Hyperhidrosis

The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with 0.9% preservative-free sterile saline (see Dilution Table). Using a 30 gauge needle, 50 Units of **BOTOX** (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine-Starch Test Procedure:
Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise, hot drinks, etc. for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 1:

Figure 1:

Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface, with the bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink, do not inject **BOTOX** directly through the ink mark to avoid a permanent tattoo effect.

2.5 Blepharospasm

For blepharospasm, reconstituted **BOTOX** is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units - 2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

The recommended dilution to achieve 1.25 Units is 50 Units/4 mL or 100 Units/8 mL; for 2.5 Units it is 50 Units/2 mL or 100 Units/4 mL (see Dilution Table).

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient-usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. Some tolerance may be found when **BOTOX** is used in treating blepharospasm if treatments are given any more frequently than every three months, and is rare to have the effect be permanent.

The cumulative dose of **BOTOX** treatment for blepharospasm in a 30-day period should not exceed 200 Units.

2.6 Strabismus

BOTOX is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for **BOTOX** injection, it is recommended that several drops of a local anesthetic and

an ocular decongestant be given several minutes prior to injection.

Note: The volume of **BOTOX** injected for treatment of strabismus should be between 0.05 - 0.15 mL per muscle.

The initial listed doses of the reconstituted **BOTOX** *[see Dosage and Administration (2.1)]* typically create paralysis of the injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

I. Initial doses in Units. Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

A. For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units - 2.5 Units in any one muscle.

B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units - 5 Units in any one muscle.

C. For persistent VI nerve palsy of one month or longer duration: 1.25 Units - 2.5 Units in the medial rectus muscle.

II. Subsequent doses for residual or recurrent strabismus.

A. It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.

B. Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.

C. Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.

D. Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.

E. The maximum recommended dose as a single injection for any one muscle is 25 Units.

The recommended dilution to achieve 1.25 Units is 50 Units/4 mL or 100 Units/8 mL; for 2.5 Units it is 50 Units/2 mL or 100 Units/4 mL (see Dilution Table).

3 DOSAGE FORMS AND STRENGTHS

Single-use, sterile 50 Units or 100 Units vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection *[see Dosage and Administration (2.1)]*.

4 CONTRAINDICATIONS

4.1 Known Hypersensitivity to Botulinum Toxin

BOTOX is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions (5.3)]*.

4.2 Infection at the Injection Site(s)

BOTOX is contraindicated in the presence of infection at the proposed injection site(s).

5 WARNINGS AND PRECAUTIONS

5.1 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Description (11)]*.

5.2 Spread of Toxin Effect

Postmarketing safety data from **BOTOX** 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, 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 the 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 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.

No definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of **BOTOX/ BOTOX** Cosmetic at the labeled dose of 20 Units (for glabellar lines) or 100 Units (for severe primary axillary hyperhidrosis) have been reported.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX** for blepharospasm at the recommended dose (30 Units and below) or for strabismus at the labeled doses have been reported.

5.3 Hypersensitivity Reactions

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

5.4 Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia

Treatment with **BOTOX** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved *[see Warnings and Precautions (5.2)]*.

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 with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

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 Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

5.5 Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of **BOTOX** *[see Adverse Reactions (6.1)]*.

5.6 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity

Patients with compromised respiratory status treated with **BOTOX** for upper limb spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in patients with stable reduced pulmonary function (defined as FEV1 40-80% of predicted value and FEV1/FVC ≤ 0.75), the event rate in change of Forced Vital Capacity $\geq 15\%$ or $\geq 20\%$ was generally greater in patients treated with **BOTOX** than in patients treated with placebo (see Table 1).

Table 1: Event rate per patient treatment cycle among patients with reduced lung function who experienced at least a 15% or 20% decrease in forced vital capacity from baseline at Week 1, 6, 12 post-injection with up to two treatment cycles with BOTOX or placebo

	BOTOX 360 Units		BOTOX 240 Units		Placebo	
	≥15%	≥20%	≥15%	≥20%	≥15%	≥20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX** *[see Warnings and Precautions (5.9)]*.

5.7 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm

Reduced blinking from **BOTOX** injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

5.8 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus

During the administration of **BOTOX** for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

5.9 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in patients treated for upper limb spasticity with **BOTOX** (3% at 251-360 Units total dose), compared to placebo (1%). In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with **BOTOX** (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%).

5.10 Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

6 ADVERSE REACTIONS

The following adverse reactions to **BOTOX** (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Contraindications (4.1) and Warnings and Precautions (5.3)]*
- Dysphagia and Breathing Difficulties in Treatment of Cervical Dystonia *[see Warnings and Precautions (5.4)]*
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity *[see Warnings and Precautions (5.9)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

BOTOX and **BOTOX** Cosmetic contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse events observed with the use of **BOTOX** Cosmetic also have the potential to be observed with the use of **BOTOX** and vice-versa.

In general, adverse events occur within the first week following injection of **BOTOX** and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions (5.2)]*.

Upper Limb Spasticity

Table 2 below lists the adverse reactions reported by ≥ 2% of **BOTOX**-treated patients and more frequent than in placebo-treated patients in double-blind, placebo-controlled clinical trials.

Table 2: Adverse Reactions Reported by ≥ 2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Adult Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	BOTOX 251-360 Units (N=115)	BOTOX 150-250 Units (N=188)	BOTOX <150 Units (N=54)	Placebo (N=182)
Gastrointestinal disorder				
Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)
General disorders and administration site conditions				
Fatigue	4 (3%)	4 (2%)	1 (2%)	0
Infections and infestations				
Bronchitis	4 (3%)	4 (2%)	0	2 (1%)
Musculoskeletal and connective tissue disorders				
Pain in extremity	7 (6%)	10 (5%)	5 (9%)	8 (4%)
Muscular weakness	0	7 (4%)	1 (2%)	2 (1%)

Cervical Dystonia

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of **BOTOX**, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Other events reported in 2 - 10% of patients in any one study in decreasing order of incidence include: increased

cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of **BOTOX** resulting from the spread of the toxin outside the injected muscles *[see Warnings and Precautions (5.2, 5.4)]*.

The most common severe adverse event associated with the use of **BOTOX** injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea *[see Warnings and Precautions (5.2, 5.4)]*. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms *[see Warnings and Precautions (5.4)]*.

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of **BOTOX** for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis
The most frequently reported adverse events (3 - 10% of adult patients) following injection of **BOTOX** in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to **BOTOX** 50 Units and 110 patients exposed to **BOTOX** 75 Units in each axilla.

Blepharospasm
In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured **BOTOX**, the most frequently reported treatment-related adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder, reduced blinking from **BOTOX** injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus
Extraocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of **BOTOX**. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%.

The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

6.2 Post-Marketing Experience

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions (5.3, 5.4)]*.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

The following events, not already addressed elsewhere in the package insert, have been reported since the drug has been marketed: abdominal pain; anorexia; brachial plexopathy; diarrhea; facial palsy; facial paresis; hyperhidrosis; hypoacusis; hypoaesthesia; localized numbness; malaise; myalgia; paresthesia; pyrexia; radiculopathy; skin rash (including erythema multiforme, and psoriasiform eruption); tinnitus; vertigo; visual disturbances; and vomiting.
Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to botulinum toxin.

6.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX** treatment by inactivating the biological activity

of the toxin. The rate of formation of neutralizing antibodies in patients receiving **BOTOX** has not been well studied.

In a phase 3 cervical dystonia study that enrolled only patients with a history of receiving **BOTOX** for multiple treatment sessions, at study entry there were 192 patients with antibody assay results, of whom 33 (17%) had a positive assay for neutralizing activity. There were 96 patients in the randomized period of the phase 3 study with valid assays at both study entry and end and who were neutralizing activity negative at entry. Of these 96, two patients (2%) converted to positive for neutralizing activity. Both of these converting patients were among the 52 who had received two **BOTOX** treatments between the two assays; none were in the group randomized to placebo in the controlled comparison period of the study.

In the randomized period of the cervical dystonia study, patients in the **BOTOX** group whose baseline assays were neutralizing antibody negative showed improvements on the Cervical Dystonia Severity Scale (CDSS) (n=64, mean CDSS change -2.1) while patients whose baseline assays were neutralizing antibody positive did not (n=14, mean CDSS change +1.1).

However, in uncontrolled studies there are also individual patients who are perceived as continuing to respond to treatments despite the presence of neutralizing activity. Not all patients who become non-responsive to **BOTOX** after an initial period of clinical response have demonstrable levels of neutralizing activity.

One patient among the 445 hyperhidrosis patients (0.2%) and two patients among the 380 adult upper limb spasticity patients (0.5%) with analyzed specimens showed the presence of neutralizing antibodies.

The data reflect the patients whose test results were considered positive or negative for neutralizing activity to **BOTOX** in a mouse protection assay. The results of these tests are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of neutralizing activity 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 neutralizing activity to **BOTOX** with the incidence reported to other products may be misleading.

The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that **BOTOX** injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

7 DRUG INTERACTIONS

No formal drug interaction studies have been conducted with **BOTOX** (onabotulinumtoxinA) for injection.

Co-administration of **BOTOX** 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.

Use of anticholinergic drugs after administration of **BOTOX** may potentiate systemic anticholinergic effects.

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **BOTOX**.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. **BOTOX** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When **BOTOX** (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately 1½ times the average high human dose for upper limb spasticity of 360 Units on a body weight basis (U/kg).

When **BOTOX** was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in

these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the average high human dose based on U/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 3 times the average high human dose based on U/kg.

8.3 Nursing Mothers

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

8.4 Pediatric Use

Spasticity

Safety and effectiveness of **BOTOX** for the treatment of spasticity have not been established in patients below the age of 18 years.

Cervical Dystonia

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Blepharospasm and Strabismus

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Axillary Hyperhydrosis

Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

Clinical studies of **BOTOX** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

Excessive doses of **BOTOX** (onabotulinumtoxinA) for injection 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 Boxed Warning and Warnings and Precautions (5.2, 5.4)]*. 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 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 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm

11 DESCRIPTION

BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain Clostridium botulinum type A, and intended for intramuscular and intradermal use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

One Unit of **BOTOX** corresponds to the calculated median intraperitoneal lethal dose (LD_{50}) in mice. The method utilized for performing the assay is specific to **Allergan's product, BOTOX**. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols for the various mouse LD_{50} assays, Units of biological activity of **BOTOX** cannot be compared to nor 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 **BOTOX** is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of **BOTOX** contains either 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride or 50 Units of Clostridium botulinum type A neurotoxin complex, 0.25 mg of Albumin Human, and 0.45 mg of

sodium chloride in a sterile, vacuum-dried form without a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or sympathetic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, **BOTOX** produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by **BOTOX**. When injected intradermally, **BOTOX** produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

12.3 Pharmacokinetics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals have not been performed to evaluate the carcinogenic potential of **BOTOX**.

Mutagenesis

BOTOX was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicologic assays.

Impairment of Fertility

In fertility studies of **BOTOX** (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males, 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the average high human dose for upper limb spasticity of 360 Units on a body weight basis (U/kg).

14 CLINICAL STUDIES

14.1 Upper Limb Spasticity

The efficacy and safety of **BOTOX** for the treatment of upper limb spasticity were evaluated in three randomized, multi-center, double-blind, placebo-controlled studies.

Study 1 included 126 patients (64 **BOTOX** and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. **BOTOX** (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 3). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 3: Study Medication Dose and Injection Sites in Study 1

Muscles Injected	Volume (mL)	BOTOX (Units)	Number of Injection Sites
Wrist			
Flexor Carpi Radialis	1	50	1
Flexor Carpi Ulnaris	1	50	1
Finger			
Flexor Digitorum Profundus	1	50	1
Flexor Digitorum Sublimis	1	50	1
Thumb			
Adductor Pollicis[a]	0.4	20	1
Flexor Pollicis Longus[a]	0.4	20	1

[a] injected only if spasticity is present in this muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

Possible scores range from 0 to 4:
0 = No increase in muscle tone (none)
1 = Slight increase in muscle tone, giving a 'catch' when the limb was moved in flexion or extension (mild)
2 = More marked increase in muscle tone but affected limb is easily flexed (moderate)
3 = Considerable increase in muscle tone - passive movement difficult (severe)
4 = Limb rigid in flexion or extension (very severe).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment

evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 4.

Table 4: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1

	BOTOX (N=64)	Placebo (N=62)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†a	-2.0*	0.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††b	-1.0*	0.0
Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale††c	-1.0	-1.0
Median Physician Global Assessment of Response to Treatment††	2.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.05$)
[a] **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles
[b] **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[c] **BOTOX** injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of **BOTOX** with placebo and included 91 patients [**BOTOX** 360 Units (N=21), **BOTOX** 180 Units (N=23), **BOTOX** 90 Units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. **BOTOX** and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 5).

Table 5: Study Medication Dose and Injection Sites in Study 2 and Study 3

	Total Dose				
Muscles Injected	**BOTOX low dose (90 Units)**	**BOTOX mid dose (180 Units)**	**BOTOX high dose (360 Units)**	**Vol. mL per site**	**Inject. Sites (n)**
Wrist Flexor Carpi Ulnaris	10 Units	20 Units	40 Units	0.4	1
Flexor Carpi Radialis	15 Units	30 Units	60 Units	0.6	1
Finger Flexor Digitorum Profundus	7.5 Units	15 Units	30 Units	0.3	1
Flexor Digitorum Sublimis	7.5 Units	15 Units	30 Units	0.3	1
Elbow Biceps Brachii	50 Units	100 Units	200 Units	0.5	4

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments.

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 6.

Table 6: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2

	BOTOX low dose (90 Units) (N=21)	BOTOX mid dose (180 Units) (N=23)	BOTOX high dose (360 Units) (N=21)	Placebo (N=26)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†b	-1.5*	-1.0*	-1.5*	-1.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††c	-0.5	-0.5	-1.0	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale††d	-0.5	-1.0*	-0.5[a]	-0.5
Median Physician Global Assessment of Response to Treatment	1.0*	1.0*	1.0*	0.0

† Primary endpoint at Week 6
†† Secondary endpoints at Week 6
* Significantly different from placebo ($p \leq 0.05$)
[a] $p=0.053$
[b] Total dose of **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of **BOTOX** injected into biceps brachii muscle

Study 3 compared 3 doses of **BOTOX** with placebo and included 88 patients [**BOTOX** 360 Units (N=23), **BOTOX** 180 Units (N=23), **BOTOX** 90 Units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger flexor tone) who were at least 6 weeks post-stroke. **BOTOX** and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 5).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 7.

Table 7: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

	BOTOX low dose (90 Units) (N=23)	**BOTOX mid dose (180 Units) (N=21)**	**BOTOX high dose (360 Units) (N=22)**	**Placebo (N=19)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale[†b]	-1.0	-1.0	-1.5*	-0.5
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale[††c]	-1.0	-1.0	-1.0*	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale[†d]	-0.5	-0.5	-1.0*	-0.5

† Primary endpoint at Week 4
†† Secondary endpoints at Week 4
* Significantly different from placebo ($p \leq 0.05$)
[b] Total dose of **BOTOX** injected into both the flexor carpi radialis and ulnaris muscles
[c] Total dose of **BOTOX** injected into the flexor digitorum profundus and flexor digitorum sublimis muscles
[d] Dose of **BOTOX** injected into biceps brachii muscle

14.2 Cervical Dystonia

A phase 3 randomized, multi-center, double-blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received **BOTOX** in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of **BOTOX**. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the **BOTOX** group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from –4 to +4 (very marked worsening to complete improvement), with 0 indicating no change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 8.

Table 8: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

	Placebo N=82	**BOTOX N=88**	**95% CI on Difference**
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3)[a,b]
% Patients with Any Improvement on Physician Global Assessment	31%	51%	(5%, 34%)[a]
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2)[c]
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0)[c]

[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.
[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included

several alternative missing data imputation methods and non-parametric statistical tests.
[c] Confidence intervals are based on the t-distribution.

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

There were several randomized studies conducted prior to the phase 3 study, which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of **BOTOX**.

In the phase 3 study the median total **BOTOX** dose in patients randomized to receive **BOTOX** (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 9. The total dose and muscles selected were tailored to meet individual patient needs.

Table 9: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles

Muscle	Number of Patients Treated in this Muscle (N=88)	Mean % Dose per Muscle	Mid-Range of % Dose per Muscle*
Splenius capitis/cervicis	83	38	25-50
Sternocleidomastoid	77	25	17-31
Levator scapulae	52	20	16-25
Trapezius	49	29	18-33
Semispinalis	16	21	13-25
Scalene	15	15	6-21
Longissimus	8	29	17-41

*The mid-range of dose is calculated as the 25th to 75th percentiles.

14.3 Primary Axillary Hyperhidrosis

The efficacy and safety of **BOTOX** for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = "underarm sweating is never noticeable and never interferes with my daily activities"; to 4 = "underarm sweating is intolerable and always interferes with my daily activities". A total of 322 patients were randomized in a 1:1:1 ratio to treatment in both axillae with either 50 Units of **BOTOX**, 75 Units of **BOTOX**, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46% to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102 mg, 123 mg, and 114 mg for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both **BOTOX** groups than in the placebo group ($p < 0.001$), but was not significantly different between the two **BOTOX** doses (see Table 10).

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in **BOTOX**-treated patients with either dose was 201 days. Among those who received a second **BOTOX** injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of **BOTOX** (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the **BOTOX** group and 36% (28/78) in the placebo group, $p < 0.001$. The difference in percentage

of responders between **BOTOX** and placebo was 55% (95% CI = 43.3, 65.9).

Table 10: Study 1 - Study Outcomes

Treatment Response	BOTOX 50 Units N= 104	BOTOX 75 Units N= 110	Place-bo N= 108	BOTOX 50-placebo (95% CI)	BOTOX 75-placebo (95% CI)
HDSS Score change ≥2 (n)[a]	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat productio n % (n)	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

[a] Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

14.4 Blepharospasm

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of **BOTOX** at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin (n=8) improved compared with the placebo group (n=4). The effects of the treatment lasted a mean of 12 weeks.

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

14.5 Strabismus

Six hundred seventy-seven patients with strabismus treated with one or more injections of **BOTOX** were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.

16 HOW SUPPLIED/STORAGE AND HANDLING

BOTOX is supplied in a single-use vial in the following sizes:

50 Units NDC 0023-3920-50

100 Units NDC 0023-1145-01

Vials of **BOTOX** have a holographic film on the vial label **that contains the name "Allergan" within horizontal lines** of rainbow color. In order to see the hologram, rotate the vial back and forth between your fingers under a desk lamp or fluorescent light source. (Note: the holographic film on the label is absent in the date/lot area.) If you do **not see the lines of rainbow color or the name "Allergan"**, do not use the product and contact Allergan for additional information at 1-800-890-4345 from 7:00 AM to 3:00 PM Pacific Time.

Storage

Unopened vials of **BOTOX** should be stored in a refrigerator (2° to 8°C) for up to 36 months for the 100 Unit vial or up to 24 months for the 50 Unit vial. Do not use after the expiration date on the vial. Administer **BOTOX** within 24 hours of reconstitution; during this period reconstituted **BOTOX** should be stored in a refrigerator (2° to 8°C). Reconstituted **BOTOX** should be clear, colorless, and free of particulate matter.

All vials, including expired vials, or equipment used with the drug should be disposed of carefully, as is done with all medical waste.

Rx Only

17 PATIENT COUNSELING INFORMATION

Provide a copy of the Medication Guide and review the contents with the patient.

17.1 Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

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 *[see Boxed Warning and Warnings and Precautions (5.2, 5.4)]*.

17.2 Ability to Operate Machinery or Vehicles

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

MEDICATION GUIDE
BOTOX®
BOTOX® Cosmetic
(Boe-tox)
(onabotulinumtoxinA)
for Injection

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

What is the most important information I should know about BOTOX and BOTOX Cosmetic?

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

- **Problems swallowing, speaking, or breathing. These problems can happen hours to weeks after an injection of BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX** or **BOTOX Cosmetic**.
- People with certain breathing problems may need to use muscles in their neck to help them breathe. These patients may be at greater risk for serious breathing problems with **BOTOX** or **BOTOX Cosmetic**.
- Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX** or **BOTOX Cosmetic** have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
    - loss of strength and muscle weakness all over the body
    - double vision
    - blurred vision and drooping eyelids
    - hoarseness or change or loss of voice (dysphonia)
    - trouble saying words clearly (dysarthria)
    - loss of bladder control
    - trouble breathing
    - trouble swallowing

These symptoms can happen hours to weeks after you receive an injection of **BOTOX** or **BOTOX Cosmetic**.

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

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines.

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles and used:

- to treat increased muscle stiffness in elbow, wrist, and finger muscles in adults with upper limb spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years and older.

BOTOX is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

BOTOX Cosmetic is a prescription medicine that is injected into muscles and used to improve the look of moderate to severe frown lines between the eyebrows (glabellar lines) in adults younger than 65 years of age for a short period of time (temporary).

It is not known whether **BOTOX** is safe or effective in children younger than:

- 18 years of age for treatment of spasticity
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe or effective for other types of muscle spasms or for severe sweating anywhere other than your armpits.

Who should not take BOTOX or BOTOX Cosmetic?

Do not take **BOTOX** or **BOTOX Cosmetic** if you:

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

What should I tell my doctor before taking BOTOX or BOTOX Cosmetic?

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

- a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- allergies to any botulinum toxin product
- had any side effect from any botulinum toxin product in the past
- a breathing problem, such as asthma or emphysema
- swallowing problems
- bleeding problems
- plans to have surgery
- had surgery on your face
- weakness of your forehead muscles, such as trouble raising your eyebrows
- drooping eyelids
- any other change in the way your face normally looks
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breast-feeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

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

Especially tell your doctor if you:

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

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

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

How should I take BOTOX or BOTOX Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles or skin.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.

What should I avoid while taking BOTOX or BOTOX Cosmetic?

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

What are the possible side effects of BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth
- discomfort or pain at the injection site
- tiredness
- headache
- neck pain
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.

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

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/5189

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	February 5, 2010
From	Eric Bastings, MD
Subject	CDTL memorandum
NDA/BLA # **Supplement #**	103000 5189
Applicant Name	Allergan
Date of Submission	September 30, 2009
PDUFA Goal Date	April 1, 2010
Proprietary Name / Established (USAN) Name	BOTOX/onabotulinumtoxinA
Dosage Forms / Strength	Intramuscular injections
Proposed Indication(s)	Treatment of spasticity
Action	*Approval*

Material Reviewed/Consulted	**Names of discipline reviewers**
Medical Officer Review	Raman Ramesh, MD and Suhail Kasim, MD
Statistical Review	Ohidul Siddiqui, Ph. D.
Pharmacology Toxicology Review	Barbara Wilcox, Ph. D.
DSI	Antoine El-Hage, Ph.D.
DRISK	Marcia Britt, Ph. D; Kendra Worthy, Pharm. D; Kendra Biddick, Pharm. D.; Suzanne Robottom, Pharm. D.
DDMAC	Amy Toscano

1. Introduction

In May 2009, the division issued a complete response letter to Allergan's BOTOX BLA efficacy supplement (sBLA) for the new indication of treatment of upper limb spasticity. In that letter, the division acknowledged that, on face, Allergan's supplement supported the efficacy and safety of BOTOX for the treatment of upper limb spasticity, but noted that the inspection of study sites of the two pivotal studies by the Division of Scientific Investigations (DSI), and the subsequent communications with Allergan identified significant issues with source data documentation. The present application is a response to FDA' action letter.

2. Background

Allergan submitted a sBLA for the new indication of treatment of upper limb spasticity on August 20, 2008.

On May 22, 2009, the division issued a complete response letter. The following issues were identified in the letter:

A. Pending REMS: On April 29, 2009, FDA requested safety labeling changes and a Risk Evaluation and Mitigation Strategy (REMS) from all sponsors of botulinum toxin marketed in the United States. The REMS was not approved at the time of 1st cycle action, and this constituted by itself a reason for not approving the efficacy supplement. The REMS and labeling changes, including a black box warning about distant spread of toxin effect have been approved since, and no longer constitute a reason to defer approval of the supplement.

B. Source data documentation: DSI could not verify the study records at one of sites of Study 191622-008 (Site 2373, from Mark Gordon, MD - New Hyde Park, NY). In addition, drug accountability records and informed consent documents could not be verified. The lack of source documents made it impossible to verify the conduct of this study site and the integrity of the data. Therefore, the data generated from this site could not be used in support of the proposed indication. On February 13, 2009, the Division held a teleconference with Allergan to address questions related to Study Site 2373. During that meeting, the Division requested Allergan's internal audit reports from Study 191622-008, as well as any additional relevant information pertaining to the general study conduct, and any source documentation currently available at Site 2373 and all other participating sites. Allergan responded to FDA that they contacted and/or visited all sites to confirm that source documents were available, and indicated that source documentation was not available in three other sites (2329, 2512 and 3009), involving an additional 14 patients. FDA acknowledged that the documentation provided by Allergan suggested that patients were indeed enrolled and studied at these sites, but concluded that the documentation was insufficient to verify the integrity of the eligibility criteria, the primary and secondary efficacy endpoints, and the occurrence of any adverse reaction in these patients. FDA asked for a third party to audit study sites in order to verify that adequate source data were available for the sites not yet inspected by the Agency or identified by Allergan as lacking adequate source data documentation. FDA also asked for a reanalysis of Study 191622-008, excluding the sites with missing source data documentation.

On August 20, 2009, Allergan submitted a complete response that included the elements requested by the Agency.

3. CMC/Device

There is no new CMC information for this efficacy supplement.

4. Nonclinical Pharmacology/Toxicology

There is no new pharmacology/toxicology information for this efficacy supplement.

5. Clinical Pharmacology/Biopharmaceutics

There is no new clinical pharmacology/biopharmaceutics information for this efficacy supplement.

6. Clinical Microbiology

There is no new clinical microbiology information for this efficacy supplement.

7. Clinical/Statistical-Efficacy

As discussed in my first cycle memorandum, Allergan conducted four primary efficacy studies, of which two were considered "pivotal" and two "supportive". These are Study 191622-008, BTOX-133/134-8051, BTOX-130-8051 and BTOX-418/422-8051.

The first cycle clinical and statistical review, as well as my memorandum contained errors in some data tables (some mean values were inavertedly replaced by median values) related to Study 191622-008, BTOX-133/134-8051, and BTOX-418/422-8051. Therefore, I include below tables with corrected values. These do not however modify my first cycle's conclusions and recommendations:

Study 191622-008 efficacy results (Week 6)

	BOTOX (N=64)	**Placebo (N=62)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale[†]	-2.0[*]	0.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale[††]	-1.0[*]	0.0
Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale[††]	-1.0	-1.0
Median Physician Global Assessment of Response to Treatment[††]	2.0[*]	0.0

[†] Primary endpoint [††] Secondary endpoints [*] Significantly different from placebo ($p \leq 0.05$)

Study BTOX-133/134-8051 efficacy results (Week 6)

	BOTOX low dose (90 Units) (N=21)	**BOTOX mid dose (180 Units) (N=23)**	**BOTOX high dose (360 Units) (N=21)**	**Placebo (N=26)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†	-1.5*	-1.0*	-1.5*	-1.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††	-0.5	-0.5	-1.0	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale††	-0.5	-1.0*	-0.5[a]	-0.5
Median Physician Global Assessment of Response to Treatment	1.0*	1.0*	1.0*	0.0

† Primary endpoint †† Secondary endpoints * Significantly different from placebo ($p \leq 0.05$) [a] p=0.053

Study BTOX-418/422-8051 efficacy results

	BOTOX low dose (90 Units) (N=23)	**BOTOX mid dose (180 Units) (N=21)**	**BOTOX high dose (360 Units) (N=22)**	**Placebo (N=19)**
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale†	-1.0	-1.0	-1.5*	-0.5
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale††	-1.0	-1.0	-1.0*	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale††	-0.5	-0.5	-1.0*	-0.5

† Primary endpoint at Week 4 †† Secondary endpoints at Week 4 * Significantly different from placebo ($p \leq 0.05$)

Pending resolution of the source data documentation issues, the first cycle review concluded that Study 191622-008 supports efficacy of BOTOX 100 U for the treatment of wrist flexors and finger flexors spasticity, and Study BTOX 133/134-8051 supports efficacy of doses 25U-100U for the treatment of wrist flexors spasticity, and 100-200U for the treatment of elbow flexors spasticity. In addition, Study BTOX-418/422-8051 supports the efficacy of a dose of 100U for the treatment of wrist spasticity, and 60 U for the treatment of finger flexors spasticity. Study BTOX-418/422-8051 failed to show a significant effect on elbow flexors spasticity. The inconsistent effect on elbow flexors may be related to the fact that investigators were not directed to inject the brachioradialis and brachialis muscles in the primary efficacy

studies. Instead, they were directed to inject only the biceps, and therefore only partially chemodenervated the muscles involved in elbow flexion. Overall, I believe that sufficient evidence of efficacy was provided for the treatment of fingers, wrists and elbow flexors.

As noted elsewhere, six sites were eventually determined not to have adequate source documentation. Dr. Siddiqui reanalyzed Study 191622-08 without these 6 sites, and confirmed that the efficacy conclusions from the re-analyzed data are similar to the efficacy conclusions from the original analysis.

8. Safety

Dr. Raman identified no safety issue that would preclude approval in his 1st cycle review. In particular, Dr. Raman did not identify any signal for spread of toxin effects at the doses recommended for treatment of upper limb spasticity. Dr. Raman also described the results of several completed studies that included pulmonary function testing in patients with spasticity, and the interim results of an ongoing study in patients with more severely compromised baseline respiratory status who received repeat treatments with BOTOX for focal upper limb spasticity (Study 191622-057). I also noted in my 1st cycle memo an apparently increased rate of upper respiratory tract infections in the BOTOX-treated group (14.3% at 360 U, 11.1% at 240 U, 6.9% placebo) in that study.

The safety update submitted with this complete response includes blinded SAE data from four ongoing GSK Japan-sponsored studies for the treatment of spasticity, and one European study sponsored by Allergan, and updated serious and non-serious adverse reactions data from Study 19622-057.

Study 191622-057 was a multi-center, double-blind, placebo-controlled, parallel group safety study of pulmonary function in patients with reduced lung function treated with BOTOX for focal upper limb spasticity due to upper motor neuron syndrome. In that study, patients (n=155) received up to two treatment cycles.

Even though decrease of vital capacity was reported as a SAE in one patient treated at 360U, as discussed by Dr. Kasim, there was no clinically meaningful difference between the BOTOX and placebo treatment groups in terms of mean changes of forced vital capacity (FVC) or Forced Expiratory Volume in 1 second (FEV1)/FVC ratio. There was however a generally higher proportion of patients with greater than 15% and greater than 20% changes in forced vital capacity in patients treated with BOTOX as compared to placebo. This justifies a new warning that patients with compromised respiratory function should be monitored closely.

The final results of Study 191622-057 also confirmed the dose-dependent increase in upper respiratory tract infections identified in the interim analysis. I reproduce below in Table 1 part of the updated Table 12-2 of Allergan's submission, that confirms the signal for a dose-dependent increase in upper respiratory tract infections (10.9% at 360U, 7.7% at 240U, and 6.3% for placebo).

Table 1: Adverse Events Regardless of Causality Reported by At Least 5% of Patients in Any Treatment Group At Any Time During Study 191622-057 (adapted from Table 12-2 of the Study Report)

	Placebo			BOTOX® 240 U			BOTOX® 360 U		
	Treatment Cycle								
System Organ Class	1st	2nd	Any	1st	2nd	Any	1st	2nd	Any
Preferred Term	(N=48)	(N=44)	(N=48)	(N=52)	(N=46)	(N=52)	(N=55)	(N=50)	(N=55)
Total Number (%) of Patients with AEs	15 (31.3%)	18 (40.9%)	25 (52.1%)	23 (44.2%)	16 (34.8%)	30 (57.7%)	21 (38.2%)	18 (36.0%)	28 (50.9%)
Infections and infestations									
Upper respiratory tract infection	2 (4.2%)	1 (2.3%)	3 (6.3%)	3 (5.8%)	1 (2.2%)	4 (7.7%)	2 (3.6%)	4 (8.0%)	6 (10.9%)

A dose-dependent signal for bronchitis was also seen in the pooled data of all controlled adult upper extremity spasticity clinical trials, as shown in Table 2 (copied from Allergan's proposed labeling):

Table 2: Adverse Reactions Reported by ≥ 2% of BOTOX-treated Patients and More Frequent than in Placebo-treated Patients in Adult Spasticity Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by Body System	BOTOX 251-360 Units (N=115)	BOTOX 150-250 Units (N=188)	BOTOX <150 Units (N =54)	Placebo (N=182)
Gastrointestinal disorder				
Nausea	3 (3%)	3 (2%)	1 (2%)	1 (1%)
General disorders and administration site conditions				
Fatigue	4 (4%)	4 (2%)	1 (2%)	0
Infections and infestations				
Bronchitis	4 (4%)	4 (2%)	0	2 (1%)
Musculoskeletal and connective tissue disorders				
Pain in extremity	7 (6%)	10 (5%)	5 (9%)	8 (4%)
Muscular weakness	0	7 (4%)	1 (2%)	2 (1%)

Table 2 also shows a dose-dependent increase in fatigue. That adverse reaction could be speculated as being linked to a "spread of toxin effect". As there was no increase in serious adverse reactions related to spread of toxin effects in BOTOX-treated patients, I do not believe that this justifies not approving this efficacy supplement.

I list in Table 3 adverse reactions that had an apparent dose-response relationship in the overall upper limb spasticity database (that includes both controlled and uncontrolled studies). Table 3 shows again a dose-dependent increase for upper respiratory tract infections, with respectively 2%, 6.6% and 8.8% in the <150U, 150 to <250U, and ≥250U treatment group. A caveat in this

table is that the studies with higher doses were generally of longer duration, and Allergan argues that this may account for some of the higher adverse reaction rates seen in the ≥250 U and 150 to 250 U dose groups. Nevertheless, the fact that the same dose-response for respiratory tract infections was also observed in controlled studies argues against that explanation. I therefore recommend that prescribers be warned of the risk of bronchitis and upper respiratory tract infections.

Of the other adverse reactions listed in Table 3, only nausea and pain in extremity were also seen to have a dose-relationship in controlled studies (as shown in Table 2).

Table 3: Adverse Events Observed In at Least 2% of Patients in the High Dose Treatment Group, and at least 1% higher in the high dose group than the mid-dose group (All BOTOX-Treated Patients in Upper Limb Studies); adapted from Table 2-1 of the safety update.

Preferred Term	BOTOX ≥250 U (N= 363)	BOTOX 150 to 250 U (N=305)	BOTOX < 150U (N=102)
Nausea	3.3%	2.3%	1%
Oedema Peripheral	5.8%	3.9%	2.9%
Urinary Tract Infection	7.7%	5.6%	2.9%
Upper Respiratory Tract Infection	8.8%	3.9%	2.9%
Nasopharyngitis	4.7%	3.6%	3.9%
Sinusitis	2.5%	1%	0%
Pneumonia	2.2%	1%	0%
Fall	6.1%	7.2%	0%
Contusion	4.1%	3%	0%
Hypercholesterolemia	3%	2.6%	0%
Pain in Extremity	8%	7.2%	4.9%
Arthralgia	3.3%	3.3%	2%
Headache	5.2%	4.6%	2.9%
Convulsion	4.4%	3.3%	0%
Balance Disorder	2.2%	0.7%	0%

Overall, I believe that the data support the safety of BOTOX for the treatment of upper limb spasticity, provided that the relevant information about spread of toxin effect, pulmonary effects of BOTOX in patients with compromised respiratory status, and the risk of bronchitis/upper respiratory tract infections are adequately described in labeling.

9. Advisory Committee Meeting

No advisory committee meeting was necessary for this efficacy supplement for an already marketed drug.

10. Pediatrics

The indication granted for this efficacy supplement will be for the treatment of upper limb spasticity, without restriction to a specific origin. Considering the focal nature of BOTOX treatment and the similarities of upper limb spasticity across conditions causing it, the Division

believes that an indication restricted to post-stroke spasticity would be pseudo-specific. As there is an adequate number of pediatric patients with spasticity of origins other than stroke (e.g. cerebral palsy), the division required in the 1st cycle action letter a revised proposed pediatric plan, to assess the safety and efficacy of BOTOX for the treatment of upper limb spasticity in pediatric patients age 2- (b) (4)

The division will waive the pediatric study requirement from birth through 23 months of age because the necessary studies are impossible or highly impracticable.

The division will defer submission of pediatric studies for ages 2 through 16 years 11 months because BOTOX is ready for approval for use in adults and the pediatric studies have not been completed. These required studies are listed below.

1: Juvenile rat toxicology study under PREA to identify the unexpected serious risk of adverse effects of BOTOX on postnatal growth and development.

2: Deferred pediatric efficacy study under PREA for the treatment of upper limb spasticity, to decrease the severity of increased muscle tone in the elbow flexors, wrist flexors and finger flexors in pediatric patients ages 2 years through 16 years 11 months.

3: Deferred pediatric long-term safety study (minimum 12 months) under PREA for the treatment of upper limb spasticity in pediatric patients ages 2 years through 16 years 11 months. The doses evaluated must be at least as high as those shown effective in the pediatric efficacy study (PMR-2), or those commonly used to treat upper limb spasticity in pediatric patients, if an effective dose is not identified in the pediatric efficacy study (PMR-2). The study must assess distant spread of toxin effects, and the effects of BOTOX on blood glucose and alkaline phosphatase. The study report must include safety information on at least 300 patients who received 2 injections over a 6-month period, with at least 100 patients who received the highest recommended dose (if any), and safety information on at least 100 patients who received 4 injections over a 12-month period, with at least 60 patients who received the highest recommended dose (if any).

11. Other Relevant Regulatory Issues

Source documentation issues

Significant source data documentation issues for Study 191622-008 were identified by DSI in the 1st review cycle. In addition to Site 2373 (Dr. Gordon; N =16), that was found by FDA to lack source data, Allergan later indicated in the 1st review cycle that three other sites involving an additional 14 patients lacked source documentation (Site 2329, 2512 and 3009). In order to address that issue, FDA asked Allergan to conduct a third party audit to verify the source data for the sites not yet inspected by the Agency or identified by Allergan as lacking adequate source data documentation.

In the complete response, Allergan identified further source data documentation issues for Site 3008 (Dr. Silver; N =5), and Site 2367 (Dr. Elovic; N=11). I could not find an explanation on

why Allergan did not identify these sites in the first cycle. The third party audit did not identify any other deficiency. Overall, there was a total of six sites with inadequate source documentation, accounting for a total of 46 patients, out of the 126 patients included in Study 191622-008.

As discussed above, exclusion of these 46 patients did not affect the conclusions of Study 1916222-08. Therefore, I consider the source data documentation issue as resolved.

Spread of toxin effects REMS, PMRs and PMCs

In May 2009, FDA issued a supplement request letter, in response to a safety review conducted on "spread of toxin effects". That letter requested a REMS (medication guide and communication plan), and the following studies to be conducted as postmarketing requirements (PMRs):

1. Juvenile rat toxicology study to identify the unexpected serious risk of adverse effects of BOTOX (botulinum toxin type A) on postnatal growth and development; this study is the same as Study 1 requested under PREA for this efficacy supplement, and completion of that study will fulfill both PMRs (i.e. the one requested in the May 2009 letter and the one requested with this action).
2. (b) (4)

(b) (4)

This efficacy supplement fulfill the PMC for the efficacy study in botulinum toxin-naive adults with upper limb spasticity. The botulinum toxin-naive efficacy study in children age 2- (b) (4) with upper limb spasticity requested as a PMC in May 2009 is now requested as PMR (Study 2) under PREA for this efficacy supplement. The May 2009 PMCs for lower extremity efficacy study in pediatric patients and adults are not affected by this supplement.

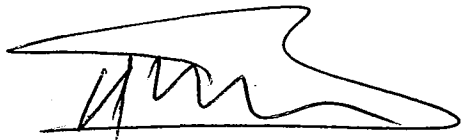
12. Labeling

This product is already approved and marketed. This application included a conversion to PLR format, which was reviewed by the various disciplines and divisions with current labeled indications (Ophthalmology and Dermatology).

In addition, the Medication guide has been slightly revised to include the new indication. The changes to the Medication Guide and to the REMS have been reviewed and accepted by Dr. Britt, Worthy, Robottom and Biddick from DRISK, and Amy Toscano from DDMAC.

13. Decision/Action/Risk Benefit Assessment

I recommend approval. The outstanding REMS issues have been resolved, and the sponsor has positively addressed the source documentation issues with the third party audit.



Eric Bastings, MD
Deputy Director,
Division of Neurology Products

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/5189

OFFICE DIRECTOR MEMO

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: February 24, 2010

From: Barbara J. Wilcox, Ph.D. Barbara Wilcox 2/24/2010

Through: Lois M. Freed, Ph.D. LMF 2/24/10

Subject: BLA 103000.5189.5004 (Resubmission 9/29/2009)

License supplement 103000.5189.5004 constitutes a complete response from the Sponsor after receipt of the Complete Response letter issued by the Agency on 5/22/2009. No new nonclinical data were submitted with this supplement. Recommendations on labeling revisions have been conveyed to the medical team. Labeling recommendations were based on:

- review of BLA 103000.5129 (Pharmacology/Toxicology Review and Evaluation, Barbara J. Wilcox, Ph.D. August, 2006)
- review (b) (4) (Pharmacology/Toxicology Review and Evaluation, Jill Merrill, Ph.D. May 5, 2009)

MEMORANDUM

DATE: March 9, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, BLA 103000/Supplement 5189

SUBJECT: Action Memo for BLA 103000/Supplement 5189, for the use of Botox (onabotulinumtoxinA) in adults with upper limb spasticity

BLA 103000/Supplement 5189, for the use of Botox (onabotulinumtoxinA) in adults with upper limb spasticity, was submitted by Allergan, Inc., on 9/29/09. The application was the subject of a Complete Response (CR) letter dated 5/22/09. The following issues were included in the CR letter:

1) a revised REMS was requested
2) the Division of Scientific Investigations (DSI) had noted the absence of source documents for one site of one of the critical controlled trials (Study 191622-008, Site 2373), and, upon the Agency's request, the sponsor identified three more sites at this study without source documents. In light of this, the division asked the sponsor in the CR letter to perform a third party audit of all sites in that study
3) the division did not grant the sponsor's request for a waiver of pediatric studies, and so required a pediatric plan for patients ages 2-(b)(4) with upper limb spasticity

The sponsor responded with a Complete Response on 9/29/09. The response has been reviewed by Dr. Suhail Kasim, medical officer, Dr. Ohidul Siddiqui, statistician, the Botox Review Team (consisting of members of DRISK, the Office of Compliance, and DDMAC), Dr. Barbara Wilcox, pharmacologist, and Dr. Eric Bastings, Neurology team leader. The review team recommends that the application be approved.

In response to the Agency's CR letter, the sponsor has submitted the results of the requested third party audit. In addition to the sites without source documentation known to us prior to the CR action, the sponsor identified 2 more sites (a total of 6) in Study 008 without source documentation, totaling 46 subjects. A re-analysis of the trial without these patients documented essentially identical results as the original analysis.

Regarding safety, the sponsor submitted the results of Study 191622-057, a randomized, placebo controlled study in patients with reduced lung function. The study examined pulmonary function tests (PFTs) in these patients. In this study,

patients were randomized to either Botox 240 U, 360 U, or placebo, and treated with two cycles, each treatment given at least 12 weeks apart.

A total of 155 patients were enrolled, and 123 completed the study. A total of 140 patients received 2 cycles of treatment.

Although there were only minor differences in the change in the median FVC from baseline between the treatment groups (see Dr. Kasim's Table 14, page 28-9), there was a dose-dependent increase in the proportion of patients with at least a 15% or 20% decrease in FVC from baseline. The following chart is taken from Dr. Kasim's Table 15, page 29:

Proportion of Patients Experiencing a Given Decrease in FVC Compared to Baseline

Treatment Cycle	Botox 360U	Botox 240U	Placebo
Cycle 1	N=55	N=52	N=48
Week 6			
>15%	7.3%	3.8%	2.1%
Week 12			
>15%	9.1%	1.9%	6.3%
>20%	5.5%	0.0%	0.0%
Cycle 2	N=50	N=46	N=44
Week 6			
>15%	6.0%	4.3%	2.3%
>20%	6.0%	2.2%	2.3%
Week 12			
>15%	12.0%	2.2%	2.3%
>20%	4.0%	2.2%	2.3%

There were no differences at Week 1 in either Cycle.

As Dr. Bastings also notes, there was a dose related increase in the incidence of upper respiratory infections: 11%, 7.7%, and 6.3% for Botox 360U, 240U, and placebo, respectively.

There were several additional deaths reported, none reasonably related to treatment except one in Study 057: a 73 year old man with multiple medical problems (including, of course, decreased pulmonary function) who was treated

with Botox 360U. At Baseline, his FVC was about 67% of predicted and his FEV1 was about 69% of predicted. Five (5) days after treatment, his FVC was 54% of predicted and his FEV1 was about 58% of predicted. He experienced a 2-3 week course of increasing dyspnea and heartburn, and died 31 days after his treatment with Botox. There were no other PFTs done. Cause of death reported by the investigator was cardiac arrest/myocardial infarction, but Dr. Kasim describes no affirmative evidence of an MI.

Safety data from other studies described revealed no new events not already known to occur with Botox. There were no serious adverse events attributable to the spread of the toxin, although there was an increased incidence of "fatigue" on Botox compared to placebo, and perhaps "muscular weakness" (see Dr. Bastings's Table 2, page 5).

With this submission, the sponsor has adequately addressed our concerns as expressed in the CR letter. There are no safety issues previously not know to be associated with Botox, and none that would preclude approval. For these reasons, then, I will issue an Approval letter, with attached agreed-upon product labeling (in particular, the results of Study 057 will be described in the Warnings and Precautions section). In addition, the letter will include, as a Post Marketing Requirement (PMR), the requirement for appropriate pediatric studies.

Russell Katz, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/5189

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

Statistical Review and Evaluation **(Addendum)**

NDA/Serial Number: BLA10300
Drug Name: BOTOX
Indication(s): Treatment of upper limb spasticity in post-stroke adult patients
Applicant: Allergan
Biometrics Division: Division 1 (HFD-710)
Statistical Reviewer: Ohidul Siddiqui, Ph.D 03/04/2010
Medical Division: HFD-120
Project Manager: Stacy Metz
Keywords: *Clinical studies, NDA review, statistical review, endpoint analysi/, multi-center, wilcoxon test*

SUMMARY

This addendum is for correcting some of the reported median values in tables (#5, #6, #7, & #8) listed the original statistical review of this NDA.

In Table 5 (for Study BTOX-133/134-8051), the correct Median Change from Baseline in Elbow Flexor Muscle Tone at Week 6 for 0 U (N=26) is -0.5.

In Table 6 (for Studies 191622-008 & BTOX-133/134-8051), the correct Median Changes from Baseline in Finger Flexor Tone at Week 6 are as follows:

Table 6. Median Changes from Baseline in Finger Flexor tone on the Ashworth Scale (ITT sample)

Dose [a]	Finger Flexor Tone (Ashworth Scale) Scale: 0 = none; 1= mild; 2= moderate; 3= severe; 4 = very severe					
	191622-008		BTOX-133/134-8051			
	100 U N=64 Median (P-value)	0 U N=62 Median	60 U N=21 Median (P-value)	30 U N=23 Median (P-value)	15 U N=21 Median (P-value)	0 U N=26 Median
Week 6	-1.0 (<0.001)	0	-0.5 (0.072)	-0.5 (0.151)	-1.0 (0.392)	-0.5

In Table 7 (for Study 191622-008), the correct Median Changes from Baseline in Thumb Flexor Tone at Week 6 are -1.0 and -1.0 for 20 U (N=36) and 0 U (N=34), respectively.

In Table 8 (for Study 191622-008), the correct Median Changes from Baseline in Physician Global Assessment at Week 6 are 2.0 and 0 for 200-240 U (N=64) and 0 U (N=62), respectively.

The remaining median changes as reported in the tables listed in the original stat review are correct.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biostatistics

Statistical Review and Evaluation (Addendum)
CLINICAL STUDIES

NDA/Serial Number:	BLA10300 (Class I Resubmission to Address Complete Response Deficiencies)
Drug Name:	BOTOX
Indication(s):	Treatment of upper limb spasticity in post-stroke adult patients
Applicant:	Allergan
Date of Document:	29 September 2009
Review Priority:	Priority
Biometrics Division:	Division 1 (HFD-710)
Statistical Reviewer:	Ohidul Siddiqui, Ph.D
Concurring Reviewers:	Kun Jin, Ph.D, Kooros Mahjoob, Ph.D
Medical Division:	HFD-120

Keywords: *Clinical studies, NDA review, statistical review, endpoint analysi, multi-center*

Introduction

The sponsor has addressed the deficiencies outlined in the 22 May 2009 Complete Response Letter. The Agency requested the sponsor to conduct a third party audit of the 191622-008 study sites to verify adequate source data documentation at the sites not inspected by the Division of Scientific Investigation. The third party conducted audits of the 13 sites. Of the 13 audited sites, source documentation was available for audit at 12 sites. One site (Site 2512, Stenehjem) did not have sufficient source documentation for any of the 6 subjects enrolled at the site. Except for one subject who did not have source documentation at Site 3005 (Marciniak), source documentation was available and verified by the auditor for all other 63 subjects at the other 12 sites. Table 1 summarizes the audit history. According to the auditor, a total of 6 sites (46/126 patients) were determined to have inadequate source documentation. In the current submission, the sponsor excluded these 46 patients from the reanalysis of the data of the study 191622-008.

Table 1: Summary of Source Documentation Status by Site

Site ID	# Subjects with Verifiable Source Documentation (Total Subjects Enrolled)	Status of Source Data
1991 (Brashear)	16 (16)	Audited by FDA - source data verifiable
2352 (Charles)	1 (1)	Audited by third party vendor - source data verifiable
2522(Cooper)	6 (6)	Audited by third party vendor - source data verifiable
2367 (Elovic)	0 (11)	Not audited by third party vendor; source data not located
2331 (Good)	4 (4)	Audited by third party vendor - source data verifiable
2373 (Gordon)	0 (16)	Audited by FDA – adequate source documentation could not be located
3002 (Graham	4 (4)	Audited by third party vendor - source data verifiable
3003 (Kassicieh)	8 (8)	Audited by third party vendor - source data verifiable

3004 (Kirsteins)	5 (6)	Audited by third party vendor - source data verifiable. Absence of AEs not documented for 1 subject.
3005 (Marciniak)	6 (7)	Audited by third party vendor - source data verifiable
2329 (Pierson)	0 (4)	Not audited by third party vendor; source data not located
2328 (Reding)	5 (5)	Audited by third party vendor - source data verifiable
3007 (Sheean)	6 (6)	Audited by third party vendor - source data verifiable
3008 (Silver)	0 (5)	Not audited by third party vendor; source data not located
2512 (Stenehjem)	0 (6)	Audited by third party vendor, adequate source documentation lacking for all subjects [b]
3009 (Subramanian)	0 (4)	Not audited by third party vendor; source data not located
3010 (Trosch)	6 (6)	Audited by third party vendor - source data verifiable
3012 (Wald)	6 (6)	Audited by third party vendor - source data verifiable [b]
3013 (Zafonte)	5 (5)	Audited by third party vendor - source data verifiable [b]

Source: 191622-008-re-ananlysis study report

Table 2 lists a summary of the subject enrollment. The re-analyzed subject sample was similar to that in the original subject sample.

Table 2: Summary of Subject Enrollment: Original Versus Re-analyzed Data

	All Subject, All sites			**Re-analyzed data**		
Exit Status	**BOTOX®**	**Placebo**	**Total**	**BOTOX®**	**Placebo**	**Total**
	(n = 64)	**(n = 62)**	**(n = 126)**	**(n = 41)**	**(n = 39)**	**(n = 80)**
Completed	64 (100%)	58 (93.5%)	122	41 (100%)	36 (92.3%)	77
Discontinued	---	4 (6.5%)	4	---	3 (7.7%)	3
Adverse events	---	1 (1.6%)	1	---	1 (2.6%)	1
Administration	---	2 (3.2%)	2	---	1 (2.6%)	1
reasons						
Protocol	---	---	---	---	---	---
violations						
Other	---	1 (1.6%)	1	---	1 (2.6%)	1

Source: 191622-008-re-ananlysis study report

The demographic data were also similar between the re-analyzed subject sample and the original subject sample. For both samples, the mean age was approximately 60, with greater than 50% of the subjects being older than 60. Both samples were similar with respect to gender and race distributions. The statistics for total dose and weight-adjusted dose injected were nearly identical between the re-analyzed subject sample and the original subject sample.

Efficacy Findings:

Table 3 lists a comparison of the efficacy findings of the primary and secondary measures for the original and re-analyzed samples. The efficacy results are consistent across the two samples.

- With regard to the Ashworth Scale Wrist Flexor Score (Primary Efficacy measure), the re-analyzed subject sample was similar to that in the original subject sample. There were statistically significant differences in both analyses at all post-treatment time points including Week 6, the primary time point.
- With regard to Physician Global Assessment Scale (key Secondary measure), the re-analyzed subject sample was similar to that in the original subject sample. There were statistically significant differences in both analyses at all post-treatment time points including Week 6, the primary time point.
- For all other secondary measures (Ashworth Scale Finger Flexor Score, Ashworth Scale Thumb Flexor Score), the reanalyzed subject sample was similar to that in the original subject sample. With regard to mean change from baseline in finger flexor Ashworth Scale scores, there were statistically significant differences in both analyses at all post-treatment time points including Week 6, the primary time point. In the mean change from baseline in thumb flexor Ashworth Scale scores, there were statistically significant differences in both analyses at all post-treatment time points except for Week 6, the primary time point.

Table 3. Mean Change from Baseline in Ashworth Scale Wrist Flexor Score (Primary and secondary Efficacy Variables): Original Versus Re-analyzed Data

	All Subjects, All Sites			**Re-analyzed Data**		
	BOTOX®	**Placebo**	**P-value**	**BOTOX®**	**Placebo**	**P-value**
	(n = 64)	**(n = 62)**		**(n = 41)**	**(n = 39)**	
Mean Change from Baseline in Ashworth Scale Wrist Flexor Score (Primary measure)						
Week 1	-1.36	-0.33	<0.001	-1.39	-0.33	<0.001
Week 4	-1.78	-0.42	<0.001	-1.86	-0.44	<0.001
Week 6 c	**-1.66**	**-0.48**	**<0.001**	**-1.58**	**-0.48**	**<0.001**
Week 8	-1.46	-0.45	<0.001	-1.48	-0.37	<0.001
Week 12	-1.07	-0.31	<0.001	-1.11	-0.28	<0.001
Physician Global Assessment Scale (Key Secondary measure)						
Week 1	1.64	0.52	<0.001	1.76	0.44	<0.001
Week 4	1.95	0.61	<0.001	1.97	0.53	<0.001
Week 6 c	**1.77**	**0.57**	**<0.001**	**1.76**	**0.48**	**<0.001**
Week 8	1.58	0.49	<0.001	1.63	0.31	<0.001

Week 12	1.09	0.50	<0.001	1.07	0.34	<0.001
Mean Change from Baseline in Ashworth Scale Finger Flexor Score						
Week 1	-1.22	-0.25	<0.001	-1.32	-0.21	<0.001
Week 4	-1.59	-0.27	<0.001	-1.74	-0.14	<0.001
Week 6 c	**-1.34**	**-0.32**	**<0.001**	**-1.41**	**-0.26**	**<0.001**
Week 8	-1.23	-0.14	<0.001	-1.33	0.00	<0.001
Week 12	-0.78	-0.12	<0.001	-0.75	-0.03	<0.001
Mean Change from Baseline in Ashworth Scale Thumb Flexor Score						
Week 1	-1.49	-0.55	<0.001	-1.56	-0.56	0.009
Week 4	-1.56	-0.42	<0.001	-1.54	-0.26	0.001
Week 6 c	**-1.31**	**-0.62**	**0.093**	**-1.25**	**-0.52**	**0.086**
Week 8	-1.20	-0.39	0.002	-1.17	-0.24	0.003
Week 12	-0.92	-0.31	0.017	-0.80	-0.05	0.019

[c] Primary timepoint; Source: 191622-008-re-ananlysis study report

FDA Reviewer's Data Analyses and Comment

This reviewer reanalyzed the original and re-analyzed samples and was able to reproduce the sponsor's submitted efficacy results for the primary and secondary efficacy measures. That is, the efficacy conclusions from the re-analyzed data are similar to the efficacy conclusions from the original analysis.

CENTER FOR DRUG EVALUATION AND RESEARCH

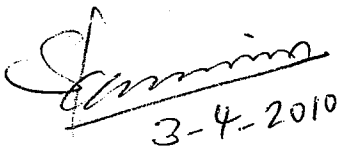
APPLICATION NUMBER:

BLA 103000/5189

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	103000/5189
Priority or Standard	Priority
Submit Date(s)	Resubmission September 29, 2009
Received Date(s)	September 30, 2009
PDUFA Goal Date	April 01, 2010
Division / Office	DNP
Reviewer Name(s)	Suhail Kasim, MD
Review Completion Date	February 12, 2010
Established Name	BOTOX OnabotulinumtoxinA
(Proposed) Trade Name	BOTOX
Therapeutic Class	Purified Neurotoxin Complex
Applicant	Allergan, Inc
Formulation(s)	Injection IM
Dosing Regimen	As needed
Indication(s)	Upper Limb Spasticity
Intended Population(s)	Adults



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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Study 191622-008 results supports efficacy of BOTOX OnabotulinumtoxinA for the treatment of wrist and finger flexors spasticity even after re-analyses of data excluding subjects from sites without adequate source documentation following the third party audit. I identified no safety issues during this review that would preclude approval.

I recommend approval with label changes.

1.2 Risk Benefit Assessment

Not applicable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

Pediatric upper limb spasticity studies in patients with spasticity between the ages of 2 years and (b) (4) (PREA).

2 Introduction and Regulatory Background

2.5 Summary of Regulatory Activity Related to Submission

On August 20, 2008 Allergan submitted supplement to biologics license application sBLA 103000/5189 proposing the use of BOTOX OnabotulinumtoxinA for the treatment of upper limb spasticity in post-stroke adult patients. Dr. Ramesh Raman reviewed the original submission submitted by Allergan on March 16, 2008. Please refer to section 2.5 Presubmission regulatory activity summarized in Dr. Ramesh Raman's review of Allergan's initial submission dated August 20, 2008.

Following review of the supplement to biologics license application, the Division sent a complete response (CR) letter to Allergan on May 22, 2009. I included below pertinent issues and reasons for not approval of the application.

1. REMS: The sponsor must incorporate applicable sections of the proposed Risk Evaluation and Mitigation Strategy under section 505-1 of the FDCA.

Reviewer comments:

On May 18, 2009 Allergan submitted amendment to April 29, 2009 FDA letter that required safety-labeling changes but could not be reviewed within the PDUFA action date. However, on July 31, 2009 Allergan proposed REMS submitted on July 27, 2009 was approved for labeled indications that included a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

2. Source data documentation: Subsequent to inspection of study sites by DSI, significant issues were identified that questioned integrity of submitted data including inability to verify source data documentation. The FDA asked Allergan to conduct a third party audit to verify adequate source data for the remaining sites not yet inspected by the Agency or identified by Allergan as lacking adequate source data documentation

3. Pediatric spasticity studies: In the sBLA submission, (b) (4) [redacted]. A waiver request for patient's age 0-23 months was acceptable.

4. Safety update should be included in the resubmission.

2.6 Other Relevant Background Information

I did not review all sections of the resubmitted supplement to biologics license application (sBLA) 103000/5189. I request the reader to please refer to Dr. Ramesh Raman's clinical review of the original submission for further information related to pertinent sections. I obtained Dr. Ramesh Raman's prior permission to refer to and to cite information included in his review of (sBLA) 103000/5189. I reviewed material identified during the resubmission pertinent to re-analysis of safety and efficacy for the use of BOTOX OnabotulinumtoxinA for the treatment of upper limb spasticity in adult patients.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Subsequent to inspection of study sites by DSI, significant issues were identified that questioned integrity of submitted data including inability to verify source data documentation. In addition to one of the two DSI inspected sites identified in Study 191622-008 (Site 2373, n=16 patients, from Mark Gordon, MD - New Hyde Park, NY), Allergan later indicated to the FDA's request for internal audit reports that three additional sites involving an additional 14 patients lacked source documentation (Site 2329, 2512 and 3009). In order to address that issue, the FDA asked Allergan to conduct a third party audit to verify adequate source data for the remaining sites not yet inspected by the Agency or identified by Allergan as lacking adequate source data documentation, and provide a reanalysis of Study 191622-008 excluding the sites with missing source data documentation.

THIRD PARTY AUDIT RESULTS

Allergan contracted with a third party vendor ((b) (4)) who conducted independent site audits. Included below is a summary of study sites status for clinical study 191622-008 to enable enumeration of calculable study subjects for re-analysis of efficacy and safety.

Table 1 BLA 103000: Study 191622-008 Summary of Source Documentation Status

Site ID	# Subjects with verifiable source documentation (Total subjects enrolled)	Status of source data
2373 (Gordon)	0 (16)	Audited by FDA - *adequate source documentation could not be located*[a]
2329 (Pierson)	0 (4)	*Not audited by third party vendor; source data not located*[c] NOTE: Allergan told FDA prior to CR letter issuance that site 2329 did not have verifiable source data
2512 (Stenehjem)	0 (6)	*Audited by third party vendor; adequate source documentation lacking for all subjects*[b] **NOTE: Allergan told FDA prior to CR letter issuance that site 2512 did not have verifiable source data. *However, THIRD PARTY AUDIT inspected this site***
3009 (Subramanian)	0 (4)	*Not audited by third party vendor; source data not located*[c] NOTE: Allergan told FDA prior to CR letter issuance that site 3009 did not have verifiable source data
[redacted]	[redacted]	[redacted]

[illegible]	[illegible]	NOTE: Allergan did not report to FDA prior to CR letter issuance that site 2367 did not have verifiable source data. Allergan indicated awareness of lack of source data in sBLA Resubmission dated September 29, 2009. Not audited or third party verified source data not located. NOTE: Allergan did not report to FDA prior to CR letter issuance that site 3008 did not have verifiable source data. Allergan indicated awareness of lack of source data in sBLA Resubmission dated September 29, 2009.
1991 (Brashear)	16 (16)	Audited by FDA - source data verifiable [a]
2352 (Charles)	1 (1)	Audited by third party vendor - source data verifiable [b]
2522 (Cooper)	6 (6)	Audited by third party vendor - source data verifiable [b]
2331 (Good)	4 (4)	Audited by third party vendor - source data verifiable [b]
3002 (Graham)	4 (4)	Audited by third party vendor - source data verifiable [b]
3003 (Kassicieh)	8 (8)	Audited by third party vendor - source data verifiable [b]
3004 (Kristeins)	5 [d] (6)	Audited by third party vendor - source data verifiable [b] Absence of AEs not documented for 1 subject.
3005 (Marciniak)	6 (7)	Audited by third party vendor - source data verifiable [b]
2328 (Reding)	5 (5)	Audited by third party vendor - source data verifiable [b]
3007 (Sheean)	6 (6)	Audited by third party vendor - source data verifiable [b]
3010 (Trosch)	6 (6)	Audited by third party vendor - source data verifiable [b]
3012 (Wald)	6 (6)	Audited by third party vendor - source data verifiable [b]
3013 (Zafonte)	5 (5)	Audited by third party vendor - source data verifiable [b]

[a] Source: FDA audit report

[b] Source: Module 5.3.5.1, (b) (4)

[c] Source: Communications from sites to Allergan

[d] Source data documentation was available for all subjects, however, for Subjects N01 and N03, source data documenting the absence of AEs was not present at the time of audit but was subsequently provided to the auditor for Subject N03. Thus, Subject N03 was included in the analysis since the data was subsequently found and satisfactorily provided to the auditor (Module 5.3.5.1, (b) (4) Page 11).

Ref: Modified Sponsor's table 2-1, page 6, section 5.3.5.1.3 Study report body 191622-008 re-analysis

The study report stated that (b) (4) audited documentation for the presence of informed consent, drug accountability, and source data for all study primary [wrist Ashworth] and secondary [Physician Global Assessment, Principal Therapeutic Intervention Target based on the Disability Assessment Scale] endpoints at each anticipated scheduled visit for 100% of the subjects. In addition, (b) (4) audited the source data for the presence or absence of adverse events. Out of 19 study sites that enrolled 126 patients, results from 46 patients could not be confirmed and were excluded from analyses. The 6 sites with inadequate source documentation included: Site 2373 (Gordon, N=16; audited by FDA), Site 2367 (Elovic, N=11), Site 2329 (Pierson, N=4), Site 3008 (Silver, N=5), Site 2512 (Stenehjem, N=6) and Site 3009 (Subramanian, N=4). Allergan contends that the inability to locate source documentation did not represent a failure to generate verifiable

source data during study conduct. Source data documentation for all subjects at these 6 sites were verified and documented in the monitoring reports during the study conduct. Allergan stated that the issue was one of record retention due to the duration of time (9 years) since the completion of the study and various other contributing factors. In Appendix 1 of the re-analyzed study report, they provided a subject-by-subject description of information found that confirmed each subject's existence and inclusion in Study 191622-008 at these 6 sites.

Reviewer comments:

In study 191622-008, 19 sites recruited 126 patients. DSI inspected two sites. One site (Site 1991, n=16 patients, Brashear) inspected by DSI had verifiable source data. The second DSI inspected site (Site 2373, n=16 patients, Gordon) lacked medical records that made it impossible to verify the conduct of the study or the data integrity due to lack of records/source documents. Allergan indicated three additional sites prior to CR letter issuance: (Site 2329, n=4, Pierson), (Site 2512, n=6, Stenehjem) and (Site 3009, n=4, Subramanian) without verifiable source data documentation.

There was inconsistency because Allergan told FDA prior to CR letter issuance that **site 2512** did not have verifiable source data, however third party audit inspected this site, which incidentally was the only additional site identified without verifiable source data.

Additional site(s) not mentioned in CR letter and which did not have third party audit included **site 3008** (site 3008, n=5, Silver), and **site 2367** (site 2367, n=Elovic). Both sites did not have third party audit because Allergan stated they became aware about lack of source data documentation at these sites as noted in the resubmission, pages 5-7 of section 5.3.5.1.3 Study report body 191622-008 re-analysis. However, it is not clear whether Allergan became aware of issues with these additional sites before or after CR letter issuance and if in fact they were aware of these additional sites prior to CR letter issuance why it was not communicated to FDA previously. Allergan explained that despite considerable effort including assistance from Allergan personnel to assess progress, contacting original principal investigators, communicating with the study conduct and retention officers at the study sites, and facilitating the retrieval of archived documents they were unable to locate source data documentation for this study and hence, were not audited by (b) (4)

In summary, no new sites were identified during the third party audit that the FDA did not have prior knowledge of. Two sites were not known to FDA at the time of CR letter issuance, and not audited by third party because Allergan became aware about lack of source data documentation. As indicated above, 6 sites that included a total of 46 subjects (n=23 Botox treated subjects, and n=23 Placebo treated subjects) were excluded from the final analysis of study 191622-008. Additionally, the *other pivotal study* did not include Investigators who enrolled patients for both studies.

Integrity of audited data

21CFR 312.62(c) Investigator Recordkeeping and retention states that records should be maintained for two years following marketing approval or until investigation are discontinued. I concur with Allergan that issues with record retention may have been due to the long interval between study completion and submission of the application. With the exclusion of sites identified the remaining sites are acceptable for inclusion in analysis.

3.2 Financial Certification and Disclosure

Financial disclosure and certification information was submitted in section 1.3.4. It included information collected for investigators and sub-investigators who participated in clinical trials (b) (4) (extension study of (b) (4)

The certification provided by Allergan had 3 components.

3.2.1 Certification Pertinent To Investigators/Sub-Investigators Who Declared That They Did Not Have Any Relevant Financial Interests

Allergan provided a list of all such investigators and sub-investigators who were involved in the above mentioned studies.

- Allergan certified that they did not enter into any financial agreement with the clinical investigators listed in the application, whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Allergan certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Allergan certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

The certifications were provided on Form 3454.

3.2.2 Certification Pertinent To Investigators/Sub-Investigators From Whom Financial Information Could Not Be Obtained

Allergan listed investigators and sub-investigators involved in studies for whom financial information could not be obtained. Allergan stated they were unable to locate the financial disclosure information in the study files and that it was deemed unreasonable to go back to these sites to collect the information because these studies were completed prior to 2002.

The certification was provided on Form 3454.

3.2.3 Certification Pertinent To Investigators/Sub-Investigators With Disclosable Financial Interests

Allergan provided list of investigators who participated in financial arrangements or held financial interests. Allergan made payments as grants to fund residency training and research, retainer for ongoing consultation, or honoraria.

The certification was provided on Form 3455.

Dr. Ramesh Raman's review noted that during evaluation of BOTOX for treatment of upper limb spasticity, four studies were considered critical for demonstrating efficacy: (b) (4). There was no information included in the submission regarding financial disclosure and certification information for study (b) (4).

Up on inquiry, Allergan informed the Division that these studies were concluded before the final rule enacted the requirement. Per both the "Amended final rule, [Federal Register: December 31, 1998 (Volume 63, Number 251)]," and the "20 March 2001 Guidance for Industry - Financial Disclosure by Clinical Investigators" the referenced documentation was required for "covered clinical studies that were ongoing on or after February 2, 1999."

Included below were the dates of study conduct indicating that the studies were concluded before the 02 February 1999 requirement.

(b) (4)
)

Reviewer's comments
It appears unlikely that the financial arrangements disclosed above introduced significant bias in to the results of the pivotal efficacy trial (b) (4) conducted with BOTOX, and submitted with this sBLA application. Two investigators without verifiable source data documentation ((b) (4)) from study (b) (4) were

already excluded from efficacy re-analysis during the resubmission. In addition these investigators either had a financial interest or failed to disclose such interests.

For the second pivotal efficacy trial (b) (4) and supportive studies (b) (4) they were conducted and concluded prior to February 2, 1999 final rule for financial disclosures by clinical investigators, and no documentation was submitted by Allergan. Since there was no requirement for providing such documentation, Allergan satisfies the financial disclosure and certification for this sBLA.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Not Applicable

5 Sources of Clinical Data

I refer the reader to Section 4.1 Sources of Clinical data, in Dr. Ramesh Raman's review of the original submission. As noted in Dr. Raman's review, out of twelve studies that evaluated BOTOX for treatment of upper limb spasticity, four studies were considered critical for demonstrating efficacy: 191622-008, BTOX-130-8051, BTOX-133/134-8051, and BTOX-418/422-8051. Please refer to the study results and reviewer comments in Dr. Raman's review.

Since study 191622-008 was audited and the data was re-analyzed following exclusion of study subjects lacking source documentation, I reviewed the resubmission that included summary of study results with the re-analyzed data from study 191622-008.

6 Review of Efficacy

Efficacy RE-ANALYSIS Summary

Allergan submitted re-analyzed study report for study 191622-008 on September 29, 2009 as recommended in the complete response letter. 6 sites that enrolled 46 patients were excluded from the final analysis (out of 126 reported in the initial study report for study 191622-008).

Allergan stated that based on the outcome of the audits by the Division and the independent auditor, the other 13 sites in the study (n = 80 subjects) had adequate

source data documentation. Allergan re-analyzed Study 191622-008 with data including only the sites with verifiable source data. Allergan stated that re-analysis did not alter the efficacy or safety conclusions and that the sample size (n = 80) within the re-analyzed dataset continued to demonstrate a statistically significant, clinically meaningful effect with BOTOX treatment. They stated that efficacy results based on re-analysis were consistent with those based on the original analysis of the full dataset (n = 126), with Ashworth scale scores for the wrist, finger, and thumb flexors demonstrating statistically significant and clinically meaningful improvements. In study 191622-008 Investigators consistently indicated better overall response in subjects who were treated with BOTOX compared with placebo as measured on the Physician Global Assessment. Allergan concluded that the clear demonstration of efficacy even with a reduction in subject sample size in this re-analysis confirmed the robustness and consistency of the treatment effect of BOTOX.

Reviewer comments

The resubmitted efficacy data for study 191622-008 was reviewed by the Agency Statistician, Dr. Ohidul Siddiqui, PhD. As indicated by Dr. Siddiqui the re-analyses of the efficacy data was reproducible and found to be consistent with Allergan's analysis. Dr. Ohidul Siddiqui's statistical review and evaluation will serve as the primary reference upon which final clinical determinations will be made. Dr. Siddiqui notes that the efficacy conclusions from the re-analyzed data are similar to the efficacy conclusions from the original analysis.

I concur with the results of the re-analysis. They are consistent with the original analyses and continue to demonstrate that treatment with BOTOX is effective at the dose levels evaluated in study 191622-008. The results are consistent with the totality of the 12 studies conducted and submitted by Allergan for this spasticity sBLA.

STUDY 191622-008 RE-ANALYSIS Submitted September 29, 2009

Patient Disposition and Demographics

In study 191622-008, 19 sites recruited 126 patients. Following the audit, 6 sites that included a total of 46 subjects (n=23 BOTOX treated subjects, and n=23 Placebo treated subjects) were excluded from the final analysis of study 191622-008. The reasons for exclusion were explained in section 3.1 of this review.

The re-analyzed subject sample and demographics were similar to the subjects originally enrolled as demonstrated in Table 3 and Table 4 below.

Table 2 Summary of Subject Enrollment: Original Versus Re-analyzed Data

	Original Data [a] (All subjects, All Sites)			Re-Analyzed Data [b]		
Exit Status	**BOTOX N=(64)**	**Placebo (N=62)**	**Total (N=126)**	**BOTOX N=(41)**	**Placebo (N=39)**	**Total (N=80)**
Completed	64 (100%)	58 (93.5%)	122	41 (100%)	36 (92.3%)	77
Discontinued	---	4(6.5%)	4	---	3 (7.7%)	3
Adverse Events	---	1 (1.6%)	1	---	1 (2.6%)	1
Administration Reasons	---	2 (3.2%)	2	---	1 (2.6%)	1
Protocol Violations	---	---	---	---	---	---
Other	---	1 (1.6%)	1	---	1 (2.6%)	1

Ref: Sponsor's Table 3-2, Section 3.1.1, Module 5.3.5.1.3
[a] Source: Module 5.3.5.1, 191622-008, Original Analysis, Table 1 (copy of table from original analysis provided in this submission).
[b] Source: Module 5.3.5.1, 191622-008, Re-analysis Table 1a. Excludes site 2329, 2367, 2373, 2512, 3008, and 3009.

Table 3 Demographics: Original Versus Re-analyzed Data

	Original Data [a] (All subjects, All Sites)			Re-Analyzed Data [b]		
	BOTOX N=(64)	**Placebo (N=62)**	**P-value**	**BOTOX N=(41)**	**Placebo (N=39)**	**P-value**
Age			0.893			0.590
Mean	61.4	61.5		62.2	60.7	
SD	14.4	13.2		14.1	15.4	
Min	23.4	22.5		23.4	22.5	
Max	88.3	87.3		80.9	87.3	
Median	60.7	62.1		62.1	63.2	
Age			0.860			0.822
<60	30 (46.9%)	28 (45.2%)		17 (41.5%)	18 (46.2%)	
≥60	34 (53.1%)	34 (54.8%)		24 (58.5%)	21 (53.8%)	
Sex			0.212			0.189
Male	28 (43.8%)	35 (56.5%)		18 (43.9%)	23 (59.0%)	
Female	36 (56.3%)	27 (43.5%)		23 (56.1%)	16 (41.0%)	
Race			0.194			0.291
Caucasian	53 (82.8%)	46 (74.2%)		33 (80.5%)	28 (71.8%)	
Black	7 (10.9%)	14 (22.6%)		5 (12.2%)	9 (23.1%)	
Asian	---	1 (1.6%)		---	1 (2.6%)	
Hispanic	3 (4.7%)	1 (1.6%)		3 (7.3%)	1 (2.6%)	
Other	1 (1.6%)	---		---	---	

Ref: Sponsor's Table 3-3, Section 3.1.2, Module 5.3.5.1.3
[a] Source: Module 5.3.5.1, 191622-008, Original Analysis, Table 3 (copy of table from original analysis provided in this submission).
[b] Source: Module 5.3.5.1, 191622-008, Re-analysis Table 3a. Excludes site 2329, 2367, 2373, 2512, 3008, and 3009.

I concur with Dr. Siddiqui's findings that the results for total dose injected and weight-adjusted dose injected were nearly identical between the re-analyzed subject sample and the original subject sample (Ref: Sponsor's Table 3-4, Section 3.1.3, Module 5.3.5.1.3). All subjects received between 200 and 240 U of BOTOX (if in the active treatment group).

Primary and Secondary Efficacy Analyses

The re-analysis of efficacy consisted of the primary (wrist flexor Ashworth) and all secondary endpoints (PGAS and the Principal Therapeutic Intervention Target [PTIT]). Other efficacy re-analyses included finger and thumb Ashworth, responder analyses, and correlation analyses.

The resubmitted efficacy data for study 191622-008 was also reviewed by Dr. Siddiqui and it was reported that the efficacy results were consistent across the two samples: original submission and re-submission, and found that the statistical findings were consistent with Allergan's reported efficacy findings.

The primary efficacy measure was the change from baseline in the wrist flexor tone assessed by the Ashworth Scale, with week 6 considered to be the primary time point. As shown in Table 5 below, the primary efficacy measure for the re-analyzed subject sample was similar to that in the original subject sample. There were statistically significant differences in both analyses at all post-treatment time points including Week 6, the primary time point.

Table 4 Mean Change from Baseline in Primary (Ashworth Scale Wrist Flexor Score) and Secondary Efficacy Variables: Original Versus Re-analyzed Data

	Original Data [a] (All Subjects, All Sites)			Re-analyzed Data [b]		
	BOTOX	**Placebo**	**P-value**	**BOTOX**	**Placebo**	**P-value**
	(N = 64)	**(N = 62)**		**(N = 41)**	**(N = 39)**	
Mean Change from Baseline in Ashworth Scale Wrist Flexor Score (Primary measure)						
Week 1	-1.36	-0.33	<0.001	-1.39	-0.33	<0.001
Week 4	-1.78	-0.42	<0.001	-1.86	-0.44	<0.001
Week 6 [c]	**-1.66**	**-0.48**	**<0.001**	**-1.58**	**-0.48**	**<0.001**
Week 8	-1.46	-0.45	<0.001	-1.48	-0.37	<0.001
Week 12	-1.07	-0.31	<0.001	-1.11	-0.28	<0.001

Physician Global Assessment Scale (Key Secondary Measure)						
Week 1	1.64	0.52	<0.001	1.76	0.44	<0.001
Week 4	1.95	0.61	<0.001	1.97	0.53	<0.001
Week 6 [c]	**1.77**	**0.57**	**<0.001**	**1.76**	**0.48**	**<0.001**
Week 8	1.58	0.49	<0.001	1.63	0.31	<0.001
Week 12	1.09	0.50	<0.001	1.07	0.34	<0.001
Mean Change from Baseline in Ashworth Scale Finger Flexor Score						
Week 1	-1.22	-0.25	<0.001	-1.32	-0.21	<0.001
Week 4	-1.59	-0.27	<0.001	-1.74	-0.14	<0.001
Week 6 [c]	**-1.34**	**-0.32**	**<0.001**	**-1.41**	**-0.26**	**<0.001**
Week 8	-1.23	-0.14	<0.001	-1.33	0.00	<0.001
Week 12	-0.78	-0.12	<0.001	-0.75	-0.03	<0.001
Mean Change from Baseline in Ashworth Scale Thumb Flexor Score						
Week 1	-1.49	-0.55	<0.001	-1.56	-0.56	0.009
Week 4	-1.56	-0.42	<0.001	-1.54	-0.26	0.001
Week 6 [c]	**-1.31**	**-0.62**	**0.093**	**-1.25**	**-0.52**	**0.086**
Week 8	-1.20	-0.39	0.002	-1.17	-0.24	0.003
Week 12	-0.92	-0.31	0.017	-0.80	-0.05	0.019

Ref: Agency Statistician Resubmission Review Table 3; Modified Sponsor's Tables 3-5, 3-6, 3-8, 3-9. Section 3.2, Module 5.3.5.1.3
Ashworth Scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe
[a] Source: Module 5.3.5.1, 191622-008, Original Analysis, (copy of tables from original analysis provided in this submission).
[b] Source: Module 5.3.5.1, 191622-008, Re-analysis, Excludes site 2329, 2367, 2373, 2512, 3008, and 3009.
[c] Primary endpoint

Physician Global Assessment (PGA) was the key secondary efficacy endpoint, and for a study to be considered to be positive an effect must be demonstrated not only on the primary efficacy endpoint, but also on the PGA. Please refer to Section 6.1.4 of Dr. Raman's review summarizing Allergan's analysis of the correlation between changes in Ashworth scores and clinical improvement at the patient level assessed by PGA, which together may be considered a clinically meaningful assessment. In the original and re-analysis, the Spearman rank correlation coefficient between the PGAS of response to treatment and wrist flexor Ashworth scale scores was found to be statistically significant at every post-treatment visit. Similar results were observed by Dr. Siddiqui in the re-analyzed subject sample and it was similar to that in the original subject sample. There were statistically significant differences in both analyses at all post-treatment time points including Week 6, the primary time point.

Similar results were observed during the re-analyses as seen during the original submission analyses for all other secondary measures: Ashworth scale finger flexor and Ashworth scale thumb flexor. Statistically significant differences were seen at all time points for finger flexors, however as observed during the original submission, the mean change from baseline in thumb flexor Ashworth Scale scores was not statistically significant in both analyses at Week 6, the primary time point.

7 Review of Safety

Safety Update Summary

The safety update at the time of resubmission included data from ongoing studies: four GSK Japan sponsored studies and two Allergan sponsored studies. Data from these studies remained blinded, and complete non-serious AE data was not available with the exception of the pulmonary safety study in patients with upper extremity spasticity with stable compromised respiratory function designed to evaluate development of further impairment from baseline after BOTOX (study 191622-057) for which the final database had been recently locked. Updated in-text tables were provided following FDA request for assessment of spirometric parameters in these patients. SAEs and deaths were reported. SAE data was summarized from the Allergan Global Pharmacovigilance and Products Complaints (GPPC) database. Allergan would not have access to the patient-specific database until the completion of the study. Since patient specific data (i.e., case report forms) were not available, narratives were not provided in this update. However, MedWatch forms generated from the GPPC database for individual patients experiencing SAEs (including deaths) were provided for the ongoing studies, which I reviewed.

The SAEs were consistent with the safety information included in the original submission and did not contribute to significant changes to the safety profile known about BOTOX, and it was unlikely that BOTOX could be attributed as the direct cause of death in the studies. Additionally, the data presented in the sBLA resubmission together with data in the original submission did not raise concerns that could be considered clinically significant to suggest systemic side effects associated with BOTOX treatment.

I concur with Allergan that based on the data currently available there was no new information that suggested significant changes in the safety profile of BOTOX for the treatment of upper limb Spasticity.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety in Resubmission

Upper-Limb spasticity study 191622-057

Ongoing study 191622-057 was a multi-center, double-blind, placebo-controlled, parallel group safety study of pulmonary function in patients with reduced lung function treated with BOTOX for focal upper limb spasticity due to upper motor neuron syndrome. The final database was recently locked in December 2009, and Allergan provided safety update of FDA requested pulmonary function test data. The study evaluated the pulmonary function safety of patients with stable compromised baseline respiratory status who received repeated treatments with BOTOX for focal upper limb spasticity. Pulmonary function test (PFT) assessments including forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) (both observed and percent predicted values), and the derived variable FEV1/FVC ratio were the primary assessments for this study. Please refer to Dr. Ramesh Raman's review for details of the pulmonary function tests and clinical significance of the measurements.

The clinical study summary shown in the table below was adapted from Allergan's submission. Please refer to Dr. Ramesh Raman's review, section 10.1 for study specific information.

Table 5 Study 191622-057

Study ID	Number of Study Centers Location	Study Start Status (Date) Enrollment Total/Goal	Design Control type	Study and Control Drugs Dose, Route and Regimen	Study Objective	# Patients by Arm Entered/ Completed	Duration	M/F mean age (range) Race	Diagnosis Inclusion Criteria	Primary Endpoint
191622-057	31 centers United States 4 centers Poland 3 centers Czech Republic 3 centers Hungary	November 2003 ongoing June 2009 155 enrolled 150 planned	multicenter double blind randomized parallel placebo control	BOTOX® 240 U or 360 U placebo IM injections into spastic upper limb muscles at physician's discretion	evaluate pulmonary function safety	Ongoing blinded BOTOX® 240 U BOTOX® 360 U Placebo	2 treatments at least 12 weeks apart	M 102 (66%) F 53 (34%) 54.4 years (18 to 83) C 107 (69%) B 28 (18%) A 1 (1%) H 18 (11%) O 1 (1%)	patients with upper limb spasticity due to upper neuron syndrome including post stroke spasticity with stable compromised baseline respiratory status	spasticity of flexor muscles (Ashworth scale) FEV1 FVC

The 2008 interim study report included unblinded data from 99 enrolled patients (29 placebo, 35 BOTOX 240 U, 35 BOTOX 360 U), some of which were ongoing at the time of the report. The last patient enrolled on January 26, 2009. At the time of the data cut-off date June 30, 2009 for this class I re-submission 155 patients completed enrollment;

123 patients completed the study, 16 patients discontinued, and 16 patients were still ongoing. The safety population included N=155 patients who received the first injection, and N=140 patients who received two treatment cycles.

Upper- and Lower-Limb spasticity study AGN/HO/SPA/001-191622

This is an ongoing multicenter, randomized, double-blind, European medical marketing reimbursement (phase 3b) study to evaluate patient outcomes and costs of managing adults with Spasticity (both upper and lower limb spasticity). Currently 260 patients are enrolled and randomly allocated 1:1 to receive either placebo + standard of care versus BOTOX <360 U+ standard of care) at baseline. All patients irrespective of original treatment assignment will receive BOTOX during the open-label phase.

Currently 260 patients are enrolled and 99 have completed the study according to the CRO. The clinical study summary is in the table below which I adapted from Allergan's submission.

Table 6 Study AGN/HO/SPA/001-191622

Study ID	Number of Study Centers, Location	Study Start Status (Date) Enrollment Total/Goal	Design Control Type	Study and Control Drugs Dose, Route and Regimen	Study Objective	# Patients by Arm Entered/ Completed	Duration	M/F Mean Age (Range) Race	Diagnosis Inclusion Criteria	Primary Endpoint
AGN/HO/SPA/001-191622	33 global sites (UK, Sweden, Germany Canada)	January 2007 ongoing 260 enrolled 99 completed 300 planned	multicentre double-blind randomize placebo-controlled	BOTOX® + standard of care BOTOX® dose range 10 to 100 U per muscle at the physician's discretion, total dosage <360 U placebo + standard of care IM injections into spastic upper and/or lower limb muscles at physician's discretion	evaluate patient outcomes and costs	ongoing blinded	52 weeks, 22 to 34 weeks of double blind treatment followed by an open-label phase	not available	patients with focal upper and/or lower limb spasticity > 3 month post stroke	number of patients who achieve their principal active functional goal

Upper-Limb spasticity study (GSK Japan) 191622-910

This was one of 2 GSK studies evaluating upper limb spasticity in Japanese patients. The open-label exploratory single-treatment 12-week study enrolled 18 patients. 6 patients each received a single treatment of either BOTOX 90 or 100 U, 180 or 200 U, and 270 or 300 U. All AEs recorded were mild to moderate in severity. There were no deaths or SAEs reported in the study.

The clinical study summary was in the table below which I adapted from Allergan's submission.

Table 7 Study (GSK Japan) 191622-910

Study ID	Number of Study Centers Location	Study Start Status (Date) Enrollment Total/Goal	Design Control Type	Study and Control Drugs Dose, Route and Regimen	Study Objective	# Patients by Arm Entered/ Completed	Duration	M/F Mean Age (Range) Race	Diagnosis Inclusion Criteria	Primary Endpoint
Study 191622-910	5 centers Japan	December 2001 complete (March 2003) 19 enrolled/ 18 planned	multicenter open-label uncontrolled stepwise * parallel * group	BOTOX® 90 or 100U, 180 or 200 U and 270 or 300 U * single intramuscular injection at the biceps brachii muscle, brachioradialis muscle, flexor carpi radialis muscle, flexor carpi ulnaris muscle, flexor digitorum profundus muscle or flexor digitorum superficialis muscle	evaluate safety and explorative evaluation of efficacy	Group 1 (BOTOX® 90 or 100 U) 6/6 Group 2 (BOTOX® 180 or 200 U) 6/6 Group 3 (BOTOX® 270 or 300 U) 6/6	1 treatment with 12 week follow up	mean age data not available	patients had post-stroke upper limb spasticity in all of the finger, hand and elbow flexor muscles	primary endpoint not specified in CSR synopsis. Efficacy endpoints: Ashworth Scale, active and passive range of joint motion, digital flexor and biceps tendon reflexes, ability to perform activities of daily living, number of finger and elbow extensions and flexions per unit time

Upper-Limb spasticity study (GSK Japan) BTX108509

It was a double-blind, placebo-controlled, multiple treatment cycle study with an open-label extension for a total duration of 48 weeks. 109 patients were enrolled to receive either placebo or BOTOX 120 or 240 U. During the open-label phase patients were administered up to 240 units repeatedly. Allergan did not have access to the translated datasets.

The clinical study summary is in the table below which I adapted from Allergan's submission.

Table 8 Study (GSK Japan) BTX108509

Study ID	Number of Study Centers Location	Study Start Status (Date) Enrollment Total/Goal	Design Control Type	Study and Control Drugs Dose, Route and Regimen	Study Objective	# Patients by Arm Entered/ Completed	Duration	M/F Mean Age (Range) Race	Diagnosis Inclusion Criteria	Primary Endpoint
BTX108509	19 centers Japan	May, 2007- complete (December, 2008) 109 enrolled/ 105 planned	part I multicenter double-blind randomized parallel group placebo controlled part II multicenter open-label uncontrolled	part I BOTOX® 200 or 240 U BOTOX® 120 or 150 U Placebo injection into 4-6 muscles total part II BOTOX® 200 or 240 U injection into 4-6 muscles total up to 3 treatment sessions	evaluate efficacy and safety	part I BOTOX® 240 U 51/47 BOTOX® 150 U 21/21 placebo 240 U 26/25 placebo 150 U 11/11 part II BOTOX® 240 U 51/38 BOTOX® 150 U 21/19 placebo 240 U 26/19 placebo 150 U 11/11	part I 1 treatment with 12 weeks follow up part II 1 treatment with 36 weeks follow up	mean age data not available	patients with upper limb spasticity at least 6 months post stroke	area under the curve for the change from baseline in the Modified Ashworth Scale wrist score in the double blind phase in the 240 U dose groups

Lower-Limb spasticity study (GSK Japan) 191622-911

This was an open-label, single-dose 12-week study that evaluated 20 patients with spastic gait due to post-stroke hemiplegia. Each patient received a single treatment session of BOTOX injection in a sequential fashion: 75 U in 7 patients (Group 1), 150 U in 7 patients (Group 2), and 225 U in 6 patients (Group 3) to the soleus muscle and gastrocnemius muscles.

The clinical study summary is in the table below which I adapted from Allergan's submission.

Table 9 Study (GSK Japan) 191622-911

Study ID	Number of Study Centers Location	Study Start Status (Date) Enrollment Total/Goal	Design Control Type	Study and Control Drugs Dose, Route and Regimen	Study Objective	# Patients by Arm Entered/ Completed	Duration	M/F Mean Age (Range) Race	Diagnosis Inclusion Criteria	Primary Endpoint
Study 191622-911	5 centers Japan	February 2002 complete (June 2003) 20 enrolled/ 18 planned	multicenter open-label uncontrolled stepwise parallel group	BOTOX® 75 or 100 U, 150 or 200 U, and 225 or 300 U single intramuscular injection at the soleus muscle and gastrocnemius muscle	evaluate safety and exploratory evaluation of efficacy	Group 1 (BOTOX® 75 or 100 U) 7/7 Group 2 (BOTOX® 150 or 200 U) 7/7 Group 3 (BOTOX® 225 or 300 U) 6/6	1 treatment with 12 week follow-up	mean age data not available	patients with spastic gait requiring the use of a walker due to post stroke hemiplegia	primary endpoint not specified in CSR synopsis Efficacy endpoints Ashworth Scale; active and passive range of joint motion, Achilles tendon reflex, ankle clonus assessment, ability to perform activities of daily living time and number of step to walk 10 m pain assessment

Lower-Limb spasticity study (GSK Japan) BTX108512

This was a double-blind, placebo-controlled study with an open-label extension for a total duration of 48 weeks (n = 120 enrolled). In the 12-week double-blind phase, a single treatment session of BOTOX at a total dose of 300 U or placebo was given. In the 36-week open-label extension, BOTOX at a total dose of 300 U was administered up to three repeated treatments.

The clinical study summary is in the table below which I adapted from Allergan's submission.

Table 10 Study (GSK Japan) BTX 108512

Study ID	Number of Study Centers Location	Study Start Status (Date) Enrollment Total/Goal	Design Control Type	Study and Control Drugs Dose, Route and Regimen	Study Objective	# Patients by Arm Entered/ Completed	Duration	M/F Mean Age (Range) Race	Diagnosis Inclusion Criteria	Primary Endpoint
BTX108512	19 centers Japan	May 2007 complete (December, 2008) 120 enrolled/ 120 planned	part I multicenter double-blind randomized parallel group placebo-controlled part II multicenter open-label uncontrolled	part I BOTOX® 300 U placebo 300 U a single IM injection into 4 muscles part II BOTOX® 300 U up to 3 treatments	evaluate efficacy and safety	part I BOTOX® 300 U 58/52 placebo 300 U 62/61 part II BOTOX® 300 U 58/45 placebo/ BOTOX® 300 U 62/52	part I 1 treatment with 12 weeks follow up part II 1 treatment with 36 weeks follow up	mean age data not available	patients with equinus deformity (plantar flexion of the ankle) at least 6 months post stroke	area under the curve for the change from baseline in Modified Ashworth Scale ankle score in the double-blind phase

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure and Adequacy of Patient Exposures for Evaluating Long Term Safety

Allergan analyzed long-term exposure from 8 out of 12 upper limb spasticity studies for doses that ranged from 25 units to 400 units. Four studies were excluded from analysis since patients received a single treatment and were followed for approximately 12 weeks.

The following summary tables include patient exposures evaluating long-term safety for the treatment of upper limb spasticity at 6-months (*2-treatments at least*) and at 1-year (*4-treatments at least*) including the highest actual dose received and duration. Exposures were counted considering the first treatment cycle as the start period.

Table 11 BLA 103000: One-Year Exposures [a]

Dose at each of 4 injections during one year	Number of Patients
400 Units or more	34
375 Units or more	49
360 Units or more	54
325 Units or more	79
300 Units or more	115
275 Units or more	125
225 Units or more	147
200 Units or more	201
150 Units or more	208
100 Units or more	212
50 Units or more	212

Ref: Modified Sponsor's Table submitted November 18, 2009
[a] 1-year: Patients exposed to 4 or more injections during the course of one year (48 weeks or 336 consecutive days), and had the specified dose at each of four injections.
Source: /statdev/BtxSafDb/Spasticity/combo/exploratory/ADHOC/FDA_sp_rq_111309.sas/ 16NOV09 09:20
SAS VERSION: 9.1

Table 12 BLA 103000: Six-Month Exposures [a]

Dose at each of 2 injections during six months	Number of Patients
400 Units or more	48
375 Units or more	66
360 Units or more	117
325 Units or more	165
300 Units or more	223
275 Units or more	235
225 Units or more	344
200 Units or more	459
150 Units or more	483
100 Units or more	487
50 Units or more	516
400 Units or more	48

Ref: Modified Sponsor's Table submitted November 18, 2009
[a] 6-months: Patients exposed to 2 or more injections during the course of six months (24 weeks or 168 consecutive days), and had the specified dose at each of two injections.
Source: /statdev/BtxSafDb/Spasticity/combo/exploratory/ADHOC/FDA_sp_rq_111309.sas/ 16NOV09 09:20
SAS VERSION: 9.1

Additionally, the sponsor provided rationale with clinical trial data as noted below to support maximum recommended cumulative dose *generally* not to exceed BOTOX 400 U anticipating that an individual patient may receive treatment for more than one indication either simultaneously or within a 3-month period, and that it was tolerated by clinical trial patients with an acceptable AE profile. In the completed controlled and open-label clinical trials for upper limb spasticity, 163/770 patients (21%) received a

maximum dose between 361 U and 400 U with 140 patients who received exactly 400 U. From combined cervical dystonia and upper limb spasticity trials 178/1519 (12%) received a maximum dose between 361 U and 400 U with 9/1519 (0.6%) patients received higher than 400 U.

Reviewer Comments

ICH E1 states that safety evaluation during clinical drug development should characterize and quantify the safety profile of a drug over a reasonable duration of time consistent with the intended long-term use of the drug. In this case, BOTOX injections intended for repeated intermittent chronic use can occur as often as 12-week intervals. As shown in tables above, there is adequate proportion of patients exposed to doses up to 360 units during the 6-month and 1-year period as initially indicated by Allergan as maximum dose for labeling during the original submission dated August 20, 2008. However, there is not sufficient proportion of exposures at the proposed highest dose of 400 units or more at 6-months and at 1-year to evaluate long-term safety in the proposed label submitted during the resubmission dated September 29, 2009. Moreover additional assessments in patients with compromised pulmonary function may be required for BOTOX dose ≥ 360U since slight although not clinical meaningful changes were observed in previous studies. The need for additional assessment of pulmonary function for BOTOX dose ≥ 360U was previously indicated to the sponsor during a teleconference with CBER in October 2002.

I recommend revision of the maximum recommended cumulative dose to include up to 360 units for treatment of upper limb spasticity since this reflects data for interpreting long-term safety with BOTOX use from clinical studies evaluating treatment of upper limb spasticity in adults.

7.3 Major Safety Results

7.3.1 Deaths

Deaths reported in the original submission.

The original submission described 10 deaths that occurred in the 12 upper limb studies (n = 770 BOTOX patients) and 3 deaths that occurred in the 4 lower limb studies (n = 266 BOTOX patients). I refer the reader to section 7.1.1 Deaths, as summarized in Dr. Ramesh Raman's review of Allergan's original submission dated August 20, 2008. None of the deaths were considered treatment-related by the Investigators. They were considered related to the progression of underlying morbidities and complications.

Deaths in ongoing Allergan studies.

Seven additional deaths were reported in sBLA 103000/5189 resubmission: one death in study 191622-057, four deaths in study AGN/HO/SPA/001-191622, and 2 deaths in GSK Japan upper limb study BTX108509.

No case-report forms were available. MedWatch forms were provided in lieu of narratives, which I had reviewed.

Table 13 BLA 103000: Deaths by Study (Updated)

Study	Death (N)	Ref
Upper Limb Studies		
BTOX-133/134-8051	1	Module 5.3.5.1.1, CSR BTOX-133/134-8051, Section 7.3.4
191622-025	3	Module 5.3.5.2, CSR 191622-025, Section 12.3.1.1
191622-056	5	Module 5.3.5.2, CSR 191622-056, Section 12.3.1.1
191622-065	1 (post study)	Module 5.3.5.1.1, CSR 191622-065, Section 12.3.1.1
191622-057	1	Module 5.3.5.4.3, CSR 191622-057, Section 12.3.1
BTX-108509	2	Module 5.3.5.3, Narratives Ongoing and GSK Studies
Lower Limb Studies		
BTOX-138/139-8051	1	Module 5.3.5.1.1, CSR BTOX-138/139-5051, Key Results
BTOX-702-8051	2 (one pre study and one post study)	Module 5.3.5.1.1, CSR BTOX-702-8051, Section 12.3.1.1
Upper and Lower Limb Studies		
AGN/HO/SPA/001-191622	4	Module 5.3.5.3, Narratives (MedWatch) Ongoing and GSK studies
Ref: Tables 2-19, 2-20, Section 2.7.4 (under heading 2.1.2); ISS Listings 2-3.1, 2-3.2, 2-3.3, 2-3.4, 2-4.1, 2-4.2, 2-4.3; Module 5.3.5.3, ISS Listings 2-1.1, 2-1.2, 2-1.3, 2-1.4, 2-2.1, 2-2.2, 2-2.3; Module 5.3.5.3, Safety Update, Section 2.1.2.2		

Narratives for Deaths

I continued the numbering sequence following Dr. Ramesh Raman's sequence of ordering of narratives for deaths in his review in section 7.1.1 Deaths, Narratives for Deaths.

14. **Patient 2329-2085 in Study 191622-057** (double-blind, placebo-controlled): (Preferred terms- Cardiac arrest; Myocardial infarction)

Patient 2329-2085 was a 73 year-old Caucasian male enrolled in study evaluating patients with reduced lung function had history of stroke, spasticity, hypercholesterolemia, hypertension, ongoing smoking history, diabetes, benign prostatic hypertrophy, and depression. He was treated with 360 U of BOTOX for upper

extremity spasticity. Baseline PFT done about 3 weeks prior to BOTOX treatment recorded FVC (2.68 L; 67% predicted) and FEV1 (2.12 L; 69% predicted) and on day of BOTOX treatment the following FVC (2.56 L; 64% predicted) and FEV1 (1.92 L; 63% predicted). PFT done 5 days after BOTOX treatment showed reduction of FVC (2.15 L; 54% predicted) and FEV1 (1.77 L; 58% predicted). There was approximately 16% decline in FVC from baseline 5 days following treatment. Following a 2-3 week clinical course of increased dyspnea and increased heartburn for which no medical attention was sought, he died 31 days after study drug treatment when he collapsed in his home and died en-route to the emergency room. No other PFT measurements were recorded in the interim until the fatal event. The Investigator noted the patient died presumably due to cardiac arrest/myocardial infarction. Autopsy was not performed. Allergan noted the event was considered serious, unexpected, not treatment related, and fatal.

The reviewer notes that PFT measurements at baseline, on day of treatment and following treatment suggests co-morbid conditions may have been contributory to declining spirometric measurements, but the CRF did not report any ongoing respiratory symptoms. However, following BOTOX treatment the 2-3 week clinical course of increasing dyspnea prior to death suggests the event may have been possibly related to BOTOX treatment at the dose administered.

15. **Patient 087/Case 0905767US in Study AGN/HO/SPA/001-191622** (double-blind, placebo-controlled): (Preferred term- Infarction; repeated infarction)

The following information was from the submitted MedWatch Form 3500A. Patient 087/Case 0905767US was a 60 year-old Caucasian male enrolled in European patient outcomes study. He had history of repeated stroke, atrial fibrillation, hypertension, diabetes, pneumonia, chronic UTI, and renal failure. He was treated with 520 U of BOTOX and died 210 days since last treatment following period of hospitalization for two weeks during management of complicated course of repeat intracerebral hemorrhage. The investigator considered the event serious, unexpected, not treatment related, and fatal.

16. **Patient 088/Case 0900923US-Case 0812605US in Study AGN/HO/SPA/001-191622**: (double-blind, placebo-controlled): (Preferred term- cerebrovascular accident)

The following information was from the submitted MedWatch Form 3500A. Patient 088/Case 0900923US-Case 0812605US was a 76 year-old Caucasian female with diabetes, hypertension, dyslipidemia, and depression died 93 days following second dose BOTOX or placebo treatment (180 U) from a cerebrovascular accident. The investigator was unable to access records from the admitting hospital. The event was considered serious, not treatment related, and fatal.

17. **Patient 122/Case 0908187US in Study AGN/HO/SPA/001-191622**: (double-blind, placebo-controlled): (Preferred term- pneumonia; community acquired pneumonia)

The following information was from the submitted MedWatch Form 3500A. Patient 122/Case 0908187US was an 81 year-old Caucasian female with history of asthma, hypertension, congestive cardiac failure, recurrent UTIs, depression and ischemic stroke. She received BOTOX treatments for lower extremity spasticity previously and last treatment was 5-months ago. On the day she received BOTOX 360 U her caregiver felt that subject was becoming increasingly short of breath on exertion. Her GP commenced her on antibiotics for treatment of lower respiratory tract infection the same day. 12 days later following hospitalization for increasing dyspnea her condition deteriorated and she died. Autopsy was not performed. The SAE listed was community acquired pneumonia. The event was considered serious, unexpected, not treatment related, and fatal.

The reviewer notes that even though she was diagnosed and being treated for respiratory infection, following BOTOX treatment the clinical course of increasing dyspnea prior to death suggests possible exacerbation of ongoing respiratory illness that could have been contributed by respiratory muscle weakness which makes the event possibly related to BOTOX treatment.

18. **Patient 166/Case 0811326US-Case 0811308US-Case 0812085US in Study AGN/HO/SPA/001-191622**: (double-blind, placebo-controlled): (Preferred term- urinary retention; femoral neck fracture; myocardial ischemia)

The following information was from the submitted MedWatch Form 3500A. Patient 166/ Case 0812085US was a 63 year-old male with history of epilepsy and diabetes, recent UTI, and fracture neck of femoral bone. He died 36 days after last 300 U placebo treatment from cardiac arrest. Autopsy identified ischemic heart disease. The event was considered serious, not treatment related, and fatal.

19. **Patient 000015/Case 0712115US in GSK Japan Study BTX108509**: (double-blind, placebo-controlled): (Preferred term- emphysema)

The following information was from the submitted MedWatch Form 3500A. Limited information was available to Allergan from the GSK Japan database. Patient 000015/Case 0712115US was a 75 year-old Asian male with history of COPD and stroke. From the report it appeared that while the patient was managed for ongoing COPD exacerbation the patient received blinded study treatments on another prior occasion. Twenty seven days following second blinded study treatment he died following brief period of hospitalization for exacerbation of chronic bronchitis when he was managed with antibiotics and bronchodilators. He died despite intubation and

artificial ventilation secondary to worsening of emphysema. The event was considered serious, not treatment related, and fatal. I concur with Allergan that ongoing COPD exacerbation may have contributed to fatal event and it was unlikely that event was possibly related to BOTOX treatment (if in fact it was the study drug administered).

20. **Patient 000193/Case 0813008US in GSK Japan Study BTX108509**: (double-blind, placebo-controlled): (Preferred term- anxiety; completed suicide)

The following information was from the submitted MedWatch Form 3500A. Patient 000193/Case 0813008US was a 58 year-old Asian male with history of hypertension, hyperlipidemia, epilepsy, diabetes, facial nerve palsy, anxiety, depression and stroke. He died 73 days after last BOTOX 240 U injection. He hung himself at his workplace. The event was considered serious, not treatment related, and fatal.

Reviewer Comment

Summary on Deaths
In concurrence with Allergan, it is unlikely that BOTOX can be attributed as the direct cause of death in these patients. There is no new information that suggests any significant change in the safety profile of BOTOX for the treatment of upper limb spasticity.

7.3.2 Nonfatal Serious Adverse Events

Upper-Limb spasticity study 191622-057
During the resubmission the clinical database for study 191622-057 remained blinded (as of June 30, 2009). However, when the database for study 191622-057 was locked and made final in late 2009 updated serious adverse events were submitted.

Serious adverse events were reported for 14.6% (7/48) patients in the placebo group, 17.3% (9/52) patients in the BOTOX 240 U group, and 10.9% (6/55) patients in the BOTOX 360 U group. The SAEs since the June 2009 report included 2 cases of hypotension, and 1 each of cellulitis (previously reported in foot note), splenic abscess, convulsion, anemia, chest pain, heart rate decreased, mobility decreased, and renal failure.

Table 14 BLA 103000: Study 191622-057 Serious Adverse Events

System Organ Class Preferred Term	Placebo (N=48)	BOTOX 240 U (N=52)	BOTOX 360 U (N=55)
Overall	**7 (14.6%)**	**9 (17.3%)**	**6 (10.9%)**
Infections & Infestations	**2 (4.2%)**	**3 (5.8%)**	**3 (5.5%)**
Abscess	0 (0.0%)	1 (1.9%)	0 (0.0%)
Acute endocarditis	0 (0.0%)	0 (0.0%)	1 (1.8%)
Appendicitis	0 (0.0%)	0 (0.0%)	1 (1.8%)
Bacteraemia	0 (0.0%)	1 (1.9%)	0 (0.0%)
Cellulitis	0 (0.0%)	1 (1.9%)	0 (0.0%)
Gastroenteritis	0 (0.0%)	0 (0.0%)	1 (1.8%)
Pneumonia	0 (0.0%)	1 (1.9%)	0 (0.0%)
Splenic abscess	1 (2.1%)	0 (0.0%)	0 (0.0%)
Wound infection	1 (2.1%)	0 (0.0%)	0 (0.0%)
Nervous System Disorders	**3 (6.3%)**	**3 (5.8%)**	**2 (3.6%)**
Convulsion	1 (2.1%)	0 (0.0%)	2 (3.6%)
Cerebral infarction	1 (2.1%)	0 (0.0%)	0 (0.0%)
Cognitive disorder	0 (0.0%)	1 (1.9%)	0 (0.0%)
Encephalitis	0 (0.0%)	1 (1.9%)	0 (0.0%)
Epilepsy	0 (0.0%)	1 (1.9%)	0 (0.0%)
Ischaemic stroke	0 (0.0%)	1 (1.9%)	0 (0.0%)
Syncope	1 (2.1%)	0 (0.0%)	0 (0.0%)
Cardiac Disorders	**1 (2.1%)**	**3 (5.8%)**	**1 (1.8%)**
Acute coronary syndrome	0 (0.0%)	1 (1.9%)	0 (0.0%)
Angina pectoris	1 (2.1%)	0 (0.0%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	0 (0.0%)	1 (1.8%)
Cardiac failure congestive	0 (0.0%)	1 (1.9%)	0 (0.0%)
Myocardial infarction	0 (0.0%)	1 (1.9%)	0 (0.0%)
Respiratory, Thoracic & Mediastinal Disorders	**1 (2.1%)**	**1 (1.9%)**	**1 (1.8%)**
Chronic obstructive pulmonary disease	1 (2.1%)	1 (1.9%)	0 (0.0%)
Dyspnoea	0 (0.0%)	0 (0.0%)	1 (1.8%)
Vascular Disorders	**1 (2.1%)**	**1 (1.9%)**	**1 (1.8%)**
Hypotension	1 (2.1%)	1 (1.9%)	0 (0.0%)
Hypertension	0 (0.0%)	0 (0.0%)	1 (1.8%)
Metabolism & Nutrition Disorders	**1 (2.1%)**	**1 (1.9%)**	**0 (0.0%)**
Hyperglycaemia	0 (0.0%)	1 (1.9%)	0 (0.0%)
Hyponatraemia	1 (2.1%)	0 (0.0%)	0 (0.0%)
Neoplasms Benign, Malignant and Unspecified (Incl. Cysts & Polyps)	**1 (2.1%)**	**0 (0.0%)**	**1 (1.8%)**
Prostate cancer	1 (2.1%)	0 (0.0%)	1 (1.8%)
Blood & Lymphatic System Disorders	**1 (2.1%)**	**0 (0.0%)**	**0 (0.0%)**
Anaemia	1 (2.1%)	0 (0.0%)	0 (0.0%)
Congenital, Familial and Genetic Disorders	**0 (0.0%)**	**1 (1.9%)**	**0 (0.0%)**
Meningocele	0 (0.0%)	1 (1.9%)	0 (0.0%)
General Disorders and Administration Site Conditions	**0 (0.0%)**	**0 (0.0%)**	**1 (1.8%)**
Chest pain	0 (0.0%)	0 (0.0%)	1 (1.8%)
Investigations	**0 (0.0%)**	**1 (1.9%)**	**0 (0.0%)**
Heart rate decreased	0 (0.0%)	1 (1.9%)	0 (0.0%)
Musculoskeletal and Connective Tissue Disorders	**1 (2.1%)**	**0 (0.0%)**	**0 (0.0%)**
Mobility decreased	1 (2.1%)	0 (0.0%)	0 (0.0%)

Renal and Urinary Disorders	**1 (2.1%)**	**0 (0.0%)**	**0 (0.0%)**
Renal failure	1 (2.1%)	0 (0.0%)	0 (0.0%)
Ref: Modified (format only) Sponsor's Updated Table 12-6 submitted following FDA Information request. Source Table 14.4-9.1 /statprod/BtxInjSps/191622057/final/Tables/tsae.sas/ 21JAN2010 SAS Version 9.1			

Upper-Limb spasticity study (GSK Japan) BTX108509
According to the GPPC database there were 27 SAEs reported for 19 patients. Two patients died: 1 case of emphysema and 1 case of completed suicide described under Module 5.3.5.3, Narratives Ongoing and GSK Studies. Only one SAE, muscular weakness was considered treatment related in a 56 year-old male whose spasticity worsened following treatment (patient 000163/Case 0804645US).

Three patients discontinued treatment due to SAEs. Patient 000005/Case 0709920US was a 75 year-old female randomized to receive placebo treatment. She fell ten days since study treatment and was subsequently withdrawn from the study during her hospitalization for management of bone fractures. Patient 000114/Case 0801881US was a 58 year-old male whose treatment administration record (BOTOX versus placebo) remained blinded and unknown, fell 57 days following study treatment. The study investigator judged the patient ineligible for further treatment following the traumatic subarachnoid hemorrhage and discontinued from the study. Patient 000140/Case 0803947US was a 73 year-old male with stroke, hypertension, and diabetes who developed repeat cerebral infarction 79 days following BOTOX administration. During the hospitalization he was withdrawn from the study.

Lower-Limb spasticity study (GSK Japan) 191622-911
There were 6 SAEs reported in 4 patients. Patient 01-2301/Case 200306534 was a 73 year old male who received 300 U BOTOX and developed gastrointestinal hypomotility, cerebral infarction, and vomiting approximately 2 weeks following treatment. GI hypomotility was possibly related to BOTOX. Patient 05-2201/Case 200212098 who was 3-years post-stoke received 200 U BOTOX and reported seizure episode 1 week following treatment during which time he had increased mobility following improvement of LL spasticity. The seizure was possibly related to study treatment. No deaths and no discontinuations due to SAEs were reported.

Lower-Limb spasticity study (GSK Japan) BTX108512
According to the GPPC database report (as of the data cut-off date of June 30, 2009), there were 18 SAEs reported for 16 patients. All SAEs were reported for only a single patient except for angina pectoris, which was reported in 2 patients who received BOTOX treatment. No consistent trends or patterns were observed in the occurrence of these SAEs in the study. There were no deaths or discontinuations reported.

I reviewed non fatal SAEs under each individual clinical study. The SAEs are consistent with the safety information included in the original submission and do not contribute to significant changes to the safety profile known about BOTOX.

7.3.3 Treatment Emergent Dropouts and/or Discontinuations

Patients who discontinued due to adverse events in the original submission and during the safety update were provided in section 5.3.5.3. Safety Update, under section 2.1.4.1.2. There were no treatment related events and the discontinuations due to adverse events were consistent with the underlying condition of the population studied.

7.3.4 Significant Adverse Events

See Section 7.3.2.

7.3.5 Submission Specific Primary Safety Concerns

Pulmonary Function Test Findings

Forced Vital Capacity (FVC)
The results in the 2009 update provided were similar to the results in the original submission in August 2008. There was a slight and inconsistent decline in FVC (L) from baseline in the BOTOX 360 U dose group. However, there were only small differences between the BOTOX dose groups and placebo in FVC change from baseline, and the range of change in terms of magnitude were similar across treatment groups without clinically meaningful differences.

The proportion of patients with FVC changes of ≥ 15% and ≥ 20% were similar during treatment cycle 1 and treatment cycle 2 suggesting no cumulative effect. A small number of patients in each treatment group experienced ≥ 15% and ≥ 20% decreases from baseline FVC during week 6 and week 12 especially in the BOTOX 360 U dose group. However, there appeared to be no pattern or consistent trend over time for clinically meaningful changes of FVC.

Table 15 PFT - Median FVC (L) At Baseline and Absolute Change from Baseline (191622-057)

Visit	BOTOX Dose Level		
	360 U	240 U	Placebo
Treatment Cycle 1	**(N = 55)**	**(N = 52)**	**(N=48)**
Baseline	2.70 L	3.07 L	2.71 L
Week 1	0.03	0.08	0.00
Week 6	-0.09	0.04	0.08
Week 12	-0.01	0.03	0.08
Treatment Cycle 2	**(N = 50)**	**(N = 46)**	**(N=44)**
Baseline	2.78 L	3.06 L	2.88 L
Week 1	-0.04	0.01	0.02
Week 6	-0.03	0.01	0.04
Week 12	-0.06	0.00	0.11
Week 18	-0.02	0.03	0.04

Ref: Modified (format only) Sponsor's Updated Table 12-6 submitted following 12-15-2009 FDA Information request

Table 16 PFT - Number (Percent) of Patients with at least 15% or 20% Decrease in FVC (L) from Baseline (191622-057)

Visit	BOTOX Dose Level		
	360 U	240 U	Placebo
Treatment Cycle 1	**(N = 55)**	**(N = 52)**	**(N=48)**
Week 1			
≥ 15%	3 (5.5%)	2 (3.8%)	5 (10.4%)
≥ 20%	0 (0.0%)	0 (0.0%)	2 (4.2%)
Week 6			
≥ 15%	4 (7.3%)	2 (3.8%)	1 (2.1%)
≥ 20%	1 (1.8%)	1 (1.9%)	1 (2.1%)
Week 12			
≥ 15%	5 (9.1%)	1 (1.9%)	3 (6.3%)
≥ 20%	3 (5.5%)	0 (0.0%)	0 (0.0%)
Treatment Cycle 2	**(N = 50)**	**(N = 46)**	**(N=44)**
Week 1			
≥ 15%	1 (2.0%)	1 (2.2%)	1 (2.3%)
≥ 20%	0 (0.0%)	0 (0.0%)	1 (2.3%)

Week 6			
≥ 15%	3 (6.0%)	2 (4.3%)	1 (2.3%)
≥ 20%	3 (6.0%)	1 (2.2%)	1 (2.3%)
Week 12			
≥ 15%	6 (12.0%)	1 (2.2%)	1 (2.3%)
≥ 20%	2 (4.0%)	1 (2.2%)	1 (2.3%)
Ref: Modified (format only) Sponsor's Updated Table 12-7 submitted following 12-15-2009 FDA Information request			

FEV1/FVC Ratio

FEV1/FVC ratio values were stable in all 3 treatment groups for the duration of the study. There were no clinically meaningful differences in the FEV1/FVC ratio change from baseline between the BOTOX groups and placebo.

Table 17 PFT - Median FEV_1/FVC Ratio (L/L) At Baseline and Absolute Change from Baseline (191622-057)

Visit	BOTOX Dose Level		
	360 U	**240 U**	**Placebo**
Treatment Cycle 1	**(N = 55)**	**(N = 52)**	**(N=48)**
Baseline	0.75	0.74	0.74
Week 1	0.00	0.00	0.00
Week 6	0.01	-0.01	0.00
Week 12	0.01	-0.01	0.01
Treatment Cycle 2	**(N = 50)**	**(N = 46)**	**(N=44)**
Baseline	0.78	0.76	0.75
Week 1	0.01	-0.01	0.00
Week 6	0.00	0.00	0.00
Week 12	0.00	-0.01	-0.02
Week 18	0.00	-0.01	-0.01
Ref: Modified (format only) Sponsor's Updated Table 12-12 submitted following 01-13-2009 FDA Information request			

Reviewer Comments

Even though there was no dose response trend for declining pulmonary function, slight decrease in FVC (L) in the higher dose BOTOX 360 U dose group compared to placebo were observed that may be suggestive of declining pulmonary function following treatment with BOTOX 360 U. Of note, at baseline the BOTOX 360 U patient group had

lower FVC with more patients in the 40-60% predicted FVC stratum suggesting that it was a more compromised group.

However, the observation that the FEV_1/FVC ratio remained almost unchanged from baseline indicated that the slight decreases in FVC was not meaningful to suggest worsening of baseline pulmonary function in the higher dose BOTOX 360 U dose group. According to the sponsor, during long-term assessment of changes in pulmonary function, changes in FVC must be ≥ 20% to ≥ 25% (Sponsor's reference Pennock et al, 1981). There were few patients in the higher dose BOTOX 360 U dose group with ≥ 20% change in FVC during expected peak effect of BOTOX and afterwards.

I concur with the sponsor that based on the safety results and PFT findings from study 191622-057, there are no changes to the known risk/benefit profile of BOTOX and the PFT analyses did not identify any patient characteristics that would indicate safety concern.

Adverse Events Potentially Associated with Systemic Effects (Pooled upper and lower limb studies)

In the original BLA submission (August 2008), Allergan provided an analysis of events of possible distant spread of toxin (PDSOT). The analysis comprised an initial screening of 24 MedDRA preferred terms. Since then, 16 additional terms were added to the 24 terms and Allergan updated the adverse event screening terms to include total of 40 terms. AEs related to the systemic effects for the pooled upper and lower limb studies were summarized in section 5.3.5.3. Safety Update, under section 2.1.5.1.1.

MedDRA preferred terms for possible distant spread of toxin *originally* included were accommodation disorder, bradycardia, botulism, constipation, diplopia, dry mouth, dysarthria, dysphagia, dysphonia, eyelid ptosis, facial palsy, facial paresis, muscular weakness, pupillary reflex impaired, paresis cranial nerve, paralysis, paralysis flaccid, pelvic floor muscle weakness, peripheral nerve palsy, peripheral paralysis, pneumonia aspiration, respiratory depression, respiratory failure, and speech disorder. In the *resubmission*, the additional terms included were aspiration, bulbar palsy, cranial nerve palsies multiple, cranial nerve paralysis, diaphragmatic paralysis, dyspnea, extraocular muscles paresis, eyelid function disorder, hyporeflexia, hypotonia, illeus paralytic, respiratory arrest, urinary retention, vision blurred, vocal cord paralysis, and vocal cord paresis.

Across the 16 clinical studies included in the ISS evaluating 1036 patients, 14 of the 40 preferred terms were reported from 13 (4.7%) patients following placebo treatment and 34 (5.9%) patients following BOTOX treatment. Patients representing 11 of these terms were addressed in the original submission (August 2008). With the expanded MedDRA

preferred term list, additional group of patients were identified representing an additional three new terms.

AEs related to the systemic effects for the pooled upper and lower limb studies are shown below.

Table 18 BLA 103000: Systemic Effects Adverse Events
Pooled Upper & Lower Limb Studies

SOC Preferred Term	Double-Blind, Placebo-Controlled		All BOTOX Treated Patients
	BOTOX	PLACEBO	
	N = 575	N = 279	N = 1036
Cardiac disorders			
Bradycardia	2 (0.3%)	0 (0.0%)	4 (0.4%)
Eye disorders			
Blurred Vision [a]	2 (0.3%)	1 (0.4%)	4 (0.4%)
Diplopia	0 (0.0%)	2 (0.7%)	1 (0.1%)
Eyelid ptosis	1 (0.2%)	0 (0.0%)	2 (0.2%)
Gastrointestinal disorders			
Constipation	7 (1.2%)	3 (1.1%)	21 (2.0%)
Dysphagia	2 (0.3%)	2 (0.7%)	3 (0.3%)
Dry mouth	1 (0.2%)	0 (0.0%)	1 (0.1%)
Musculoskeletal & CT disorders			
Muscular weakness	9 (1.6%)	2 (0.7%)	27 (2.6%)
Nervous system disorders			
Hypotonia [a]	1 (0.2%)	0 (0.0%)	2 (0.2%)
Facial palsy	0 (0.0%)	0 (0.0%)	1 (0.1%)
Speech disorder	0 (0.0%)	0 (0.0%)	1 (0.1%)
Renal and Urinary disorders			
Urinary retention [a]	3 (0.5%)	1 (0.4%)	5 (0.5%)
Resp., Thoracic & Med disorders			
Pneumonia aspiration	1 (0.2%)	0 (0.0%)	8 (0.8%)
Respiratory failure	0 (0.0%)	0 (0.0%)	2 (0.2%)

Ref: Table 2-19, 2.1.5.1.2; Module 5.3.5.3, Safety Update
Original Submission (August 2008), Module 5.3.5.3, ISS Table 4-7.7, ISS Table 4-7.8
[a] Adverse events from the expanded 40 MedDRA terms for possible distant spread of toxin

As discussed in Dr. Ramesh Raman's review, the only events with an incidence greater than 1% with BOTOX in the placebo-controlled, double-blind studies were constipation and muscular weakness. The narratives during the resubmission are included in section 5.3.5.3. Safety Update, under section 2.1.5.1.3.

Reviewer comments

Blurred Vision

Four patients reported this event: two patients were randomized to BOTOX treatment, 1 patient to placebo treatment, and 1 patient in an open label extension study. In all cases, in concurrence with Allergan, the events were unlikely caused by BOTOX considering the time to onset and transient symptoms in presence of co-morbid illness.

Hypotonia

The two cases represented hypotonia in patients enrolled in the upper limb studies. Both patients had decreased tone in focal muscle groups on the hemiparetic side. In concurrence with Allergan, the events were local effects due to known BOTOX pharmacologic effects.

Urinary retention

Of the four cases identified, in concurrence with Allergan, the urinary symptoms were not related to BOTOX treatment. Two patients at risk for prostate hypertrophy with concurrent medical illnesses developed urinary retention several months after BOTOX treatments. One patient died from cardiac arrest (Patient 2328-213/BTOX134-8051) during hospitalization for evaluation of urinary retention. The investigator did not consider the event treatment related considering the time course of onset of symptoms and co-morbidities. Another patient with co-morbid illnesses and history of neurogenic bladder developed urinary retention several months after BOTOX treatment, which resolved spontaneously and had negative re-challenge with no further complaints.

In summary, the data presented in the sBLA resubmission together with data in the original submission did not raise concerns that could be considered clinically significant to suggest systemic side effects associated with BOTOX treatment.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events in the Ongoing Allergan Studies and GSK Japan Studies

For Allergan study AGN/HO/SPA/001-191622 unblinded non-serious AE data was not available. Common adverse event data was not available for the two GSK Japan studies, BTX108509 and BTX108512. GSK has a licensing agreement with Allergan for the development and marketing of BOTOX for the treatment of spasticity and GSK was currently pursuing an indication in Japan. The sponsor stated that the case report forms

were in Japanese. English versions of the final reports and datasets were not available as of the data cut-off date of June 30, 2009. Therefore, there are no events to report that would affect safety of the product in labeling.

Allergan informed FDA during a teleconference in December 2009 that for study 191622-057 final database was recently locked. Updated AE data was provided. Since the interim report (20 August 2008) the MedDRA terms were updated (from version 10.1 to 12.0) and the denominator in calculating the event rate for the 2nd treatment cycle reflected the patients who had a 2nd injection (as opposed to all patients).

The reviewer notes that in study 191622-057 higher percentage of patients treated with BOTOX 360 U experienced upper respiratory tract infections compared to placebo across the treatment groups and between treatment cycles. I indicated earlier in section 7.3.5, there appeared to be no pattern or consistent trend over time for clinically meaningful changes of FVC measurements and the PFT analyses did not identify any patient characteristics that would indicate new safety concern.

However, these clinically observed results suggest that there may be dose dependent increase of upper respiratory tract infections together with a cumulative effect with BOTOX 360 U dose. This is plausible given that higher BOTOX doses administered to patients with reduced lung function may further exacerbate or cause respiratory compromise leading to pulmonary complications and SAEs which may not be evident from PFT measurements, and therefore higher dose BOTOX must include clinical monitoring for ongoing respiratory illness or further respiratory decline in patients with compromised respiratory status.

Table 19 BLA 103000/ Study 191622-057 Adverse Events for at least 5% in Any Treatment Group

SOC Preferred Term	BOTOX 360 U			BOTOX 240 U			PLACEBO		
	TREATMENT CYCLE								
	1ST N=55	2ND N=50	Any N=55	1ST N=52	2ND N=46	Any N=52	1ST N=48	2ND N=44	Any N=48
Total number (%) of patients with AEs	21 (38.2%)	18 (36.0%)	28 (50.9%)	23 (44.2%)	16 (34.8%)	30 (57.7%)	15 (31.3%)	18 (40.9%)	25 (52.1%)
Infections and Infestations Upper Respiratory Tract Infection	2 (3.6%)	4 (8.0%)	6 (10.9%)	3 (5.8%)	1 (2.2%)	4 (7.7%)	2 (4.2%)	1 (2.3%)	3 (6.3%)
Gastrointestinal Disorders									
Diarrhea	2 (3.6%)	0 (0%)	2 (3.6%)	1 (1.9%)	0 (0%)	1 (1.9%)	2 (4.2%)	2 (4.5%)	4 (8.3%)
Vomiting	1 (1.8%)	0 (0%)	1 (1.8%)	1 (1.9%)	0 (0%)	1 (1.9%)	1 (2.1%)	2 (4.5%)	3 (6.3%)
Nervous system Disorders Headache	1 (1.8%)	2 (4.0%)	3 (5.5%)	0 (0%)	0 (0%)	0 (0%)	1 (2.1%)	2 (4.5%)	3 (6.3%)
Muscle Spasticity	0 (0%)	0 (0%)	0 (0%)	3 (5.8%)	0 (0%)	3 (5.8%)	0 (0%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders Musculoskeletal Pain	2 (3.6%)	1 (2.0%)	3 (5.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2.3%)	1 (2.1%)
Pain in Extremity	1 (1.8%)	1 (2.0%)	2 (3.6%)	2 (3.8%)	1 (2.2%)	3 (5.8%)	0 (0%)	2 (4.5%)	2 (4.2%)
Respiratory, thoracic and mediastinal disorders									
Cough	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)	2 (4.3%)	3 (5.8%)	0 (0%)	2 (4.5%)	2 (4.2%)

Ref: Modified (format only) Sponsor's Updated Table 12-2 submitted following 01-13-2009 FDA Information request

7.4.2 Laboratory Findings

For the two ongoing Allergan-sponsored trials (191622-057 and AGN/HO/SPA/001-191622) and the four GSK Japan studies (191622-910, 191611-911, BTX108509, BTX108512) datasets were not available which would allow for the analysis of clinical laboratory findings.

7.4.5 Special Safety Studies/Clinical Trials

For the two ongoing Allergan-sponsored trials (191622-057 and AGN/HO/SPA/001-191622) and the four GSK Japan studies (191622-910, 191611-911, BTX108509, BTX108512) datasets were not available which would allow for the analysis of safety in special groups and situations. There was no further pooled data available to comment

on pulmonary safety since ongoing study results for study 191622-057 remained blinded.

Adverse Events in Studies from the Literature

An updated search strategy identical to that used in the original submission was conducted by Allergan identifying publications between March 2008 and June 2009 that cited Botulinum toxin (any serotype) describing studies and case reports for the treatment of post-stroke Spasticity in the upper limb or the lower limb.

Module 5.3.5.3 Safety Update Table 5-1 and Module 5.4 BOTOX Spasticity Literature Search Results: Upper Limb summarized 15 published articles describing the treatment of 739 patients with upper limb spasticity due to stroke (or other diagnoses), including 2 studies that did not differentiate upper limb from lower limb. Four of the studies were randomized, placebo-controlled. Eight studies were open-label, and there were three case reports. Safety was not reported in seven of the studies. In eight studies, 586 patients received BOTOX and 22 patients received Dysport®. The dose of BOTOX and the location and frequency of injections differed among the studies reported in the literature, and was often individualized to fit patient requirements. Doses of BOTOX reported in these studies ranged from 75 U to 500 U.

No adverse events were reported in 7 upper limb studies with 131 patients. Adverse events reported in the other eight studies of 608 patients, including published results from study 191622-056 previously submitted to the sBLA during original submission were transitory muscle weakness and pain/discomfort or bruising at the injection site. In addition, the following events were reported in more than one patient treated with BOTOX: somnolence (N=4/20), tiredness/fatigue (N=4/20), and headache (N=2/20) (Allergan ref. Simpson et al, 2009). One patient previously treated repeatedly with BOTOX doses up 700 units developed contralateral weakness and fatigue 2 weeks after receiving BOTOX 800 units. Although there was gradual clinical resolution, subsequent lowered doses up to 490 units at four more visits was tolerated until a repeat injection of 500 units reproduced the contralateral symptoms once again, which resolved within 4 weeks (Allergan ref. Varghese-Kroll and Elovic, 2009). No systemic or severe adverse events were noted in any of these upper limb studies. No deaths were reported.

Module 5.3.5.3 Safety Update Table 5-2 and Module 5.4 BOTOX Spasticity Literature Search Results: Lower Limb summarized 5 literature studies describing the treatment of 97 patients with only lower limb spasticity due to stroke (or other diagnoses). One of the studies was randomized and blinded; 4 studies were open-label. Adverse events were not mentioned in four of the studies. In the study with safety data, 22 cases of transient pain and one other case of pruritus were reported in 34 patients treated with BOTOX 300 U. No systemic side effects were noted in any of these lower limb studies. No deaths were reported.

I concur with Allergan that based on the data currently available there is no new information that suggests any significant changes in the safety profile of BOTOX for the treatment of upper limb Spasticity.

8 Postmarket Experience

This is an update to section 7.1.17 Postmarketing Experience, discussed under Dr. Ramesh Raman's review of the original submission.

Worldwide Approval History

"As of June 30, 2009, BOTOX is approved in 78 countries and marketed in 70 countries. BOTOX is licensed globally for a range of indications, but not all indications are licensed in all countries.

BOTOX was first approved on 29 December 1989 in the United States (US) and is now marketed worldwide for the treatment of a variety of disorders under the brand names BOTOX®, BOTOX® COSMETIC, VISTABEL®,VISTABEX® and BOTOX® Vista.

Approved indications worldwide for BOTOX include cervical dystonia, blepharospasm, hemifacial spasm, focal dystonias, strabismus, equinus foot deformity due to spasticity in pediatric cerebral palsy patients, focal spasticity, upper limb spasticity associated with stroke, spasmodic dysphonia, achalasia, axillary hyperhidrosis, and cosmetic treatment of facial wrinkles. In a few countries, BOTOX is approved for the treatment of essential tremor, anal fissure, and migraine and/or tension type headache. In the US, BOTOX is approved for strabismus/blepharospasm/VII nerve disorder (approved 1989), cervical dystonia (approved 2000), hyperhidrosis (approved 2004), and BOTOX COSMETIC for glabellar lines (approved 2002).

As of June 30, 2009, BOTOX COSMETIC was approved in 33 countries and marketed in 16 countries. In the European region, the cosmetic formulation is approved under the tradename VISTABEL® or VISTABEX®. The Marketing Authorization Holder in Japan for BOTOX and BOTOX Vista is GlaxoSmithKline KK."

Summary of Postmarketing Findings (Updated)

The most recent sixteenth periodic safety update report summarized safety information from worldwide sources from January 01, 2009 up to June 30, 2009. During the 2009 reporting period, no changes were made to the Company Core Data Sheet (CCDS). An updated version of the CCDS (CCDS version 14) is in development. The FDA approved REMS on July 31, 2009 is being implemented.

I reviewed the fatal and serious events reported during the period, and it did not have new safety information. Allergan states that it's Global Safety database (as of May 31, 2009) includes a total of 13,209 adverse event cases following therapeutic use of BoNT-A (1,349 serious and 11,860 non-serious) and 16,066 following cosmetic use (304 serious and 15,762 non-serious) reported from launch to current.

Patient Exposure (Updated January 01-June 30 2009)

Please refer to section 7.1.17 of Dr. Ramesh Raman's review for details prior to this reporting period. Allergan estimated (b) (4) cosmetic and (b) (4) therapeutic treatment sessions in the United States between January 01, 2009 up to June 30, 2009. According to Allergan, assuming (b) (4) treatment sessions per patient per year for a cosmetic indication and (b) treatment sessions per patient per year for a therapeutic indication, patient exposure is estimated at (b) (4) patient-years for cosmetic indications and (b) (4) patient-years for therapeutic indications as summarized in the tables below.

Table 20 BLA 103000: Patient Exposure USA

(Jan 01, 2009 to June 30, 2009)

Indication	(b) (4)
Therapeutic Diagnosis	
Movement Disorders	
Adult Spasticity	
Pediatric Spasticity	
Headache	
Pain	
Gastrointestinal/Genitourinary	
Hyperhidrosis	
Cosmetic Diagnosis	

Ref: Modified Sponsor's Table 5-3, Section 5, Module 5.3.6. Periodic Safety Update Report (Jan 2009-Jun 2009) - Spasticity

Table 21 BLA 103000: Patient Exposure by Region

(Jan 01, 2009 to June 30, 2009)

Region		(b) (4)
EU		
USA		
Rest of the World		

Ref: Modified Sponsor's Table 5-4, Section 5, Module 5.3.6. Periodic Safety Update Report (Jan 2009-Jun 2009) - Spasticity

Summary of Regulatory Authority or Allergan Actions Taken for Safety Reasons

Allergan stated that between January 01, 2004 and June 30, 2009, there were no new marketing authorization application rejections, no license suspensions, and no distribution restrictions for safety reasons. Allergan submitted actions relating to safety issues that were taken by Regulatory Authorities or by Allergan.

Table 22 BLA 103000: Regulatory Authority or Allergan Actions Taken for Safety Reasons

Event	Country/ Region	Action Taken	Date
Theoretical risk of transmissible spongiform encephalopathy (TSE) to humans for all medicinal products in Japan that contained or were derived from bovine materials.	Japan	Per request of the Japanese Ministry of Health, Labour and Welfare (MHLW) Allergan (via GlaxoSmithKline K.K.) disseminated a "Dear Doctor" letter to all BOTOX physicians in Japan advising them that bovine-derived components (obtained from US materials) are used in part of the manufacturing process of BOTOX; Japanese labeling is updated to include this safety information under General Precautions.	Jan 2005-Dec 2005
Potential for adverse events due to spread of toxin to sites distant from the area of injection.	EU	Following numerous discussions with EU regulatory authorities including AFSSAPS (VISTABEL® RMS) and IMB (BOTOX RMS) and also the Pharmacovigilance Working Party (PhVWP) between June 2005 and April 2007, Allergan submitted a comprehensive BOTOX RMP dated 30 September 2007 (Version 1.0) to the relevant EU regulatory authorities. PhVWP agreed with EU Marketing Authorization Holders (MAH's) on the definition of possible distant spread of toxin. Revisions to the label to provide additional warnings regarding possible distant spread of toxin were made to the SPCs for all Botulinum toxin products in Europe and to the BOTOX Company Core Data Sheet (CCDS). As part of the RMP, a joint MAH EU Dear Health Professional Communication (DHPC) on the issue of spread of toxin was agreed in June 2007 and distribution began in July 2007	June 2005-Sept 2007
	US	In the US Allergan submitted an analysis to FDA on possible spread of toxin for adults and pediatrics.	December 2007

		The FDA notified the public in an "Early Communication" that Botulinum toxin products have been linked in some cases to adverse reactions, including respiratory failure and death, following treatment of a variety of conditions using a wide range of doses.	February 2008
Possible Distant Spread of Toxin (PDSOT)	US	In the US, in regards to possible distant spread of toxin, Allergan submitted revised draft US Package Inserts for BOTOX and BOTOX COSMETIC, and a Dear Doctor Letter for BOTOX.	March - April 2008
	China	Per SFDA request Allergan submitted general product and prescribing information, safety information (including specifications, safety/efficacy information, AE case report profiles, and risk management measures), and evaluation reports of risk/benefit. Allergan provide information from submissions to other regulatory agencies	March - April 2008
	Japan	Allergan provided PMDA with a chronology of all interactions with the FDA and EU Health Authorities regarding possible distant spread of toxin	March - April 2008
	Singapore	Allergan submitted to the Singapore HA information on possible distant spread of toxin	November 2008
	Canada	Allergan submitted possible distant spread of toxin data to Health Canada to support changes to the Product Monographs. Health Canada requested Allergan draft a Healthcare Professional Communication (HPC) in collaboration with them to be posted on Health Canada's website (PSUR #15). This information has now been posted to Health Canada's website.	Nov - Dec 2008
Fatal case reported in Switzerland of a child who died within 20 hours of administration of the Botulinum toxin product BOTOX for JCP (Case0802187US Feb 2008).	Switzerland	At the request of Swissmedic, a DHPC was sent to all doctors and pharmacists who purchase BOTOX and Dysport® in Switzerland. This letter encompassed both Botulinum toxin type A products on the Swiss market (BOTOX, Dysport®).	March - April 2008
	Ireland	In Ireland, in response to the fatal pediatric case in Switzerland, the IMB requested additional information on the use in children of BOTOX, including an overall assessment of benefit/risk, analyses concerning the use of concomitant sedation or general anesthesia, and suspected interactions in adults and children. Information was submitted to IMB on April 18th, 2008. Report was submitted to FDA on May 2nd, 2008	March-April 2008
	France	AFSSAPS requested the following detailed analyses: all cases of death reported with BOTOX, serious cases reported in children, cases linked to a spread of the toxin beyond the injection site in children, and a summary of data from the literature concerning pharmacovigilance for Botulinum toxin type A use in children.	April-May 2008

		Allergan provided AFSSAPS with the detailed analyses requested in May 2008 as well as a proposed revision of the SPC. Submission data was similar to data presented to IMB and FDA	
Safety relevant variation approved	Switzerland	Safety relevant changes of the prescribing information regarding warnings in children with cerebral palsy and overdose were approved.	Feb 2009
Update to the USPI	US	The FDA requested that several warnings be strengthened in the BOTOX and BOTOX Cosmetic labels including the effects of possible distant spread of toxin and the lack of interchangeability between Botulinum Toxin products. Allergan has complied and safety labeling updated.	FDA approved July 2009
Implementation of a Risk Evaluation and Mitigation Strategy (REMS)	US	At the request of the FDA a REMS program will be implemented and includes the following components: patient medication guide and physician communication plan. Allergan has complied, and the REMS approved by FDA.	FDA approved July 2009
Additional Post marketing requirements and commitments	US	At the request of the FDA, Allergan will be conducting additional clinical and non-clinical studies	Submitted to FDA May 2009
Ref: Table 2-1, Section 2.1, Module 5.3.6. Post-marketing Safety Summary			

Summary of Safety labeling Changes to BOTOX Effective May 22, 2009

Allergan stated that the following updates to the *BOTOX USPI draft* were made as part of the safety labeling change request from the FDA in May 2009. The following table submitted by Allergan contains a summary of safety labeling changes made.

Table 23 BLA 103000: Safety changes to BOTOX USPI, FDA May 22, 2009

Section of BOTOX USPI	Summary of Updates
Highlights: Dosage and Administration	Updated maximum cumulative dose
Highlights: Adverse Reactions	Updated to include events >5% and > placebo for all indications
Boxed Warning	Updated to include adult spasticity
Dosage and Administration	Updated maximum cumulative dose Updated to include specific dilution instructions for all indications
Warnings and Precautions	Updated to include safety language from BL 10300-5120 regarding: BOTOX and BOTOX Cosmetic containing the same active ingredient, injection-related adverse events, and vasovagal responses due to needle-related pain. Updated to include reactions >2% and > placebo broken down by levels of exposure for Upper Limb Spasticity

Adverse Reactions: Post-Marketing Experience	Updated to include reports of new onset or recurrent seizures Updated to include the following post-marketing events: abdominal pain; anorexia; brachial plexopathy; diarrhea; facial palsy; facial paresis; hyperhidrosis; hypoacusis; hypoaesthesia; localized numbness; malaise; myalgia; myasthenia gravis; paresthesia; pruritus; pyrexia; radiculopathy; skin rash (including erythema multiforme, urticaria, and psoriasiform eruption); (b) (4); tinnitus; vertigo; visual disturbances; and vomiting.
Ref: Module 5.3.6. Post-marketing Safety Summary, Sponsor's Table 2-3, Section 2.3.	

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/5189

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	December 3, 2009
To:	Russell Katz, MD, Director Division of Neurology Products (DNP)
Thru:	Mary Willy, PhD, Deputy Director Division of Risk Management (DRISK)
From:	BOTOX Review Team Marcia Britt, PhD., Health Education Reviewer (DRISK) Kendra Worthy, Pharm.D., Drug Risk Management Analyst (DRISK) Suzanne Berkman Robottom, Pharm.D., Team Leader (DRISK) Kendra Biddick, Consumer Safety Officer, Office of Compliance Amy Toscano, Professional Reviewer, Division of Drugs, Marketing and Communication (DDMAC)
Subject:	Modification of Botox REMS in response to Complete Response Submission
Drug Name(s):	Botox® (onabotulinumtoxinA)
Submission Number:	5189
Application Type/Number:	BLA 103000
Applicant/sponsor:	Allergan, Inc.
OSE RCM #:	2009-2009

1 INTRODUCTION AND BACKGROUND

This review follows a request from the Division of Neurology Products (DNP) for the Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK) to review and comment on the modified Risk Evaluation and Mitigation Strategy (REMS) for Botox (onabotulinumtoxinA).

The REMS for Botox was approved on July 31, 2009 to address the risk(s) of medication errors related to the lack of interchangeability of Botox units and the spread of toxin effect beyond the injection site. The REMS consists of a Medication Guide, Communication Plan (Dear Healthcare Provider Letter disseminated within 6 weeks of REMS approval), and Timetable for Assessment (18 months, 3 years, and 7 years) of the REMS. Similar REMS are approved for all currently marketed botulinum toxin products to address these risks as they affect the entire class.

Allergen received a Complete Response on May 22, 2009 for the upper limb spasticity indication. The approved REMS application included indications for cervical dystonia in adults, severe primary axillary hyperhidrosis and the treatment of strabismus and blepharospasm associated with dystonia. The sponsor provided a Class I resubmission on September 29, 2009 to address, in full, the deficiencies outlined in the CR. The resubmission included a proposed modification to the Botox REMS.

2 MATERIAL REVIEWED

The following document(s) were reviewed:

- Allergan's Proposed REMS Modification submission with the addition of Botox Upper Limb Spasticity Indication submitted September 29, 2009.
- Allergan's BOTOX REMS approved on July 31, 2009 with the following components:
  - Supporting Document
  - Dear Healthcare Provider Letter
- www.botoxmedical.com
- Risk Evaluation and Mitigation Strategy video; https://hcp.botoxmedical.com/botox-information/Pages/rems-program.aspx

3 DISCUSSION

The addition of this indication to the Botox label has limited impact on the approved REMS, warranting only a change to the text of the Medication Guide. The Timetable for Assessment of the REMS should remain consistent with the timetable in the original REMS approval. With regard to the DHCP letter, it was to be mailed within 6 weeks of the REMS approval and that obligation has been met. Therefore, it is not necessary to revise a DHCP letter that has already been disseminated. We identified no further revisions or modifications.

We do note that Allergan created a section of the Botox product website directed at healthcare professionals describing the REMS. This section includes a link to view a video to "Learn about the REMS program for BOTOX". Neither the REMS webpage nor the video were included as part of the July 31, 2009 REMS approval. Therefore, these would be considered promotional.

DDMAC and Office of Compliance have been made aware of the video. Allergan did not request DDMAC advisory comments on this video. From a regulatory perspective, Allergan is not required to submit such a piece prior to using it, if it were a strictly promotional piece. Allergan's

only regulatory responsibility is to submit the video at the time of first use to DDMAC via Form 2253.

Because the video is currently in circulation, Allergan should be instructed to revise the video to remove any representation that it is part of the approved REMS (as this is not part of the approved REMS) and submit it to DDMAC via Form 2253 since it would be considered a promotional piece.

Comments to DNP

The Division of Risk Management and the OSE BOTOX Review Team find the modified REMS for Botox (onabotulinumtoxinA) acceptable once the sponsor accepts the recommended changes in the REMS document (see Appendix A).

The Medication Guide review will be provided under a separate cover.

Comments to Sponsor

1) The Agency has recently been made aware of the "Learn about the REMS program for BOTOX" video on the onabotulinumtoxinA website. The Agency did not review or approve the webpage or content of the video prior to it being placed on the onaboutlinumtoxinA website as part of the REMS approval. We remind you that REMS materials are subject to approval by the Agency and must be submitted and approved prior to dissemination.

- Revise the website and the content of the video to remove any reference that the video is part of the approved REMS.
- Submit the video to DDMAC using Form 2253 or request a modification with an assessment to the approved REMS for consideration to include in the REMS.

2) The timing of the assessment of the REMS should remain consistent with the original approval date of the REMS (see Appendix A).

3) The surveys for the planned assessments require no modification at this time.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: December 04, 2009

To: Russell Katz, MD, Director
Division of Neurology Products

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management

From: LaShawn Griffiths, MSHS-PH, BSN, RN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management

Shawna Hutchins, BSN, RN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide),

Drug Name(s): Botox Cosmetic (onabotulinumtoxin A) for Injection

Application Type/Number: BLA 103000

Supplement Number: 5189

Applicant/sponsor: Allergan Inc.

OSE RCM #: 2009-2009

1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Botox® Cosmetics (onabotulinumtoxin A).

Botox® Cosmetics was initially approved in 1989; supplement number 5189 is being submitted for an added indication of upper limb spasticity in post-stroke adult patients.

Please let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant. The proposed REMS is being reviewed by DRISK and will be provided to DNP under separate cover.

2 MATERIAL REVIEWED

- Draft BOTOX® COSMETICS (onabotulinumtoxin A) Prescribing Information (PI) submitted May 19, 2009 and revised by the Review Division throughout the current review cycle.
- Draft BOTOX® COSMETICS (onabotulinumtoxin A) Medication Guide (MG) submitted on May 18, 2009.

3 RESULTS OF REVIEW

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

Our annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/5189

OTHER REVIEW(S)

CENTER FOR DRUG EVALUATION AND RESEARCH

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III
Division of Dermatology and Dental Product
Silver Spring MD 20993

Tel: 301 796-2110
Fax: 301 796-9894

RECEIVED FEB 0 1 2010

MEMORANDUM

Date: Jan 19, 2010

From: Jane Liedtka, M.D., Medical Officer, DDDP

Through: Jill Lindstrom, M.D., Dermatology Team Leader, DDDP
Susan Walker, M.D., Division Director, DDDP

1/27/10

To: Russell Katz, M.D., Director, Division of Neuropharmacological Drug Products (DNDP),

Cc: Julie Beitz, M.D., Office Director, ODE 3, CDER

Re: DDDP Consult #1230 – Botox PLR Conversion

Material Reviewed:

Summary Review for Regulatory Action – BLA 103000/5189, May 22, 2009
Annotated-draft-labeling-text-spasticity submitted with 29SEP09 Resubmission
Gov sj brief
Botox Labeling approved 8/2009

Background:

DNP received a labeling supplement for Botox on August 20, 2008. The sponsor, Allergan, is seeking a new indication for the treatment of upper limb spasticity in post-stroke patients for Botox. This supplement has triggered PLR conversion.

The Botox label includes an indication held in the Dermatology division, Axillary Hyperhidrosis; therefore DNP has requested DDDP input on the following sections of PLR labeling: HIGHLIGHTS OF PRESCRIBING INFORMATION and under FULL PRESCRIBING INFORMATION

1.3 INDICATIONS AND USAGE- Primary Axillary Hyperhidrosis

2.4 DOSAGE AND ADMINISTRATION- Primary Axillary Hyperhidrosis
6.1 ADVERSE REACTIONS- Primary Axillary Hyperhidrosis
8.4 USE IN SPECIFIC POPULATIONS-Pediatric Use- Axillary Hyperhydrosis
14.3 CLINICAL STUDIES - Primary Axillary Hyperhidrosis

Discussion/Review:

HIGHLIGHTS OF PRESCRIBING INFORMATION

In the DOSAGE AND ADMINISTRATION section of "Highlights" the sponsor uses the term axillary (b) (4)", this should be replaced by the term axillary "hyperhydrosis".

In the ADVERSE REACTIONS section of "Highlights" the sponsor lists the following under axillary hyperhidrosis: injection site pain, non-axillary sweating, pharyngitis, flu syndrome. I would recommend adding "and hemorrhage" after injection site pain to the list of adverse reactions.

FULL PRESCRIBING INFORMATION

In Section 1.3 INDICATIONS AND USAGE under **Primary Axillary Hyperhidrosis,** the sentence "Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively" references unapproved indications. This statement has been in the existing label and does convey safety information that may be of use to the prescriber. It is not customary for DDDP to reference unapproved indications but since the scope of the PLR label conversion does not include reassessing content I do not recommend removal of the statement at this time.

In Section 1.3 INDICATIONS AND USAGE under **Primary Axillary Hyperhidrosis,** I recommend adding the sentence, "Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18 (b) (4) ."

In Section 2.4 DOSAGE AND ADMINISTRATION under **Primary Axillary Hyperhidrosis**, I find the sponsor's proposal acceptable.

In Section 6.1 ADVERSE REACTIONS under **Primary Axillary Hyperhidrosis**, I find the sponsor's proposal acceptable.

In Section 8.4 USE IN SPECIFIC POPULATIONS-Pediatric Use- **Axillary Hyperhydrosis,** I find the sponsor's proposal acceptable.

In Section 14.3 CLINICAL STUDIES under **Primary Axillary Hyperhidrosis**, I find the sponsor's proposal acceptable.

37 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA 103000/5189

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103000

COMPLETED APR 2 9 2009

Allergan, Inc.
Attention: Melina M. Dass, MS, RAC Manager
Regulatory Operations and Intelligence
2525 Dupont Drive
Irvine, CA 92612-1599

Dear Ms. Dass:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Botox/Botox Cosmetic (botulinum toxin Type A).

Sections 505(o)(4), 505-1, and 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) provide FDA with new authorities to require sponsors of approved drugs to make safety related labeling changes (section 505(o)(4) of the FDCA), develop and comply with Risk Evaluation and Mitigation Strategies (REMS) (section 505-1 of the FDCA), and conduct postmarketing studies and clinical trials (section 505(o)(3) of the FDCA) based upon new safety information that becomes available after approval of the drug.

Since Botox/Botox Cosmetic (botulinum toxin Type A) was approved in 1989, we have become aware of new safety information indicating that the use of botulinum toxin products, including Botox/Botox Cosmetic (botulinum toxin Type A), have been associated with the spread of toxin effects from the site of injection to distant sites causing generalized weakness, resulting in hospitalization and, in some cases, death. We have also received postmarketing reports of patients who had received botulinum toxin injections in the head, neck and shoulder areas having symptoms of dysphagia, ptosis, and difficulty holding their heads up. These symptoms are consistent with the local spread of botulinum toxin. Respiratory problems after botulinum toxin injections have also been reported.

Because there are other marketed botulinum toxin products with different dose to potency ratios, we are concerned about medication errors from interchanging the products. Some botulinum toxin products will have different units of dosing, even for the same indication such as cervical dystonia. We have determined that medication errors including overdosing and underdosing can occur due to the potential for healthcare providers to substitute one product for another and interchange dose units, and we have received postmarketing reports associated with overdoses. We consider this to be additional "new safety information" as defined in FDAAA.

We believe that the new safety information should be included in the labeling of Botox/Botox Cosmetic (botulinum toxin Type A). We have also determined that a REMS is necessary for the drug to ensure that the benefits of the drug outweigh the risks. Finally, we are requiring you to

conduct postmarketing studies and clinical trials to assess and identify serious risks. These requirements are described more fully below.

In addition, we request that you submit your new established name, approved by USAN, for consideration by the Agency. The name change should be submitted as a prior approval supplement.

SAFETY LABELING CHANGES

In accordance with section 505(o)(4) of the FDCA, we are notifying you that based on the new safety information described above, we believe that the new safety information should be included in the labeling for Botox/Botox Cosmetic (botulinum toxin Type A) in the specified sections as follows:

BOXED WARNING

Distant Spread of Toxin Effect

Postmarketing reports indicate that the effects of Botox/Botox Cosmetic 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.

CLINICAL PHARMACOLOGY

Pharmacokinetics

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

~~Botulinum Toxin Type A is not expected to be present in the peripheral blood at measurable levels following IM or intradermal injection at the recommended doses. The recommended quantities of neurotoxin administered at each treatment session are not expected to result in systemic, overt distant clinical effects, i.e. muscle weakness, in patients without other neuromuscular dysfunction. However, sub-clinical systemic effects have been shown by single-fiber electromyography after IM doses of botulinum toxins appropriate to produce clinically observable local muscle weakness.~~

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of Botox/Botox Cosmetic are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of Botox/Botox Cosmetic 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 Botox/Botox Cosmetic 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 Botox and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or swallowing. When distant effects occur, additional respiratory muscles may be involved (see *Warnings*).

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several weeks, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

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 post marketing 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 Warnings, 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 Botox/Botox Cosmetic [*see Adverse Reactions*].

OVERDOSAGE

Excessive doses of Botox/Botox Cosmetic 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.

[Note to sponsor: add any information related to overdoses in your clinical studies.]

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://www.cdc.gov/ncidod/srp/drugs/drug-service.html.

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, blurred vision or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

MEDICATION GUIDE

In addition to the changes described above to the labeling, you should submit a proposed Medication Guide for this product. Enclosed is a draft Medication Guide that contains what we consider to be the necessary information to inform patients of the increased risk of distant spread of botulinum toxin effects, and the potential for medication errors related to the lack of

interchangeability of Botox/Botox Cosmetic (botulinum toxin type A) with other licensed botulinum toxin products.

Under 21 CFR 208.24(d), you are also responsible for ensuring that the label of each container or package, where the container label is too small, includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is to be provided. The safety labeling changes portion of the supplement should contain marked up package or container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- "Dispense the enclosed Medication Guide to each patient." or
- "Dispense the accompanying Medication Guide to each patient."

In accordance with section 505(o)(4), within 30 days of the date of this letter, you must submit a prior-approval supplement proposing changes to the approved labeling in accordance with the above direction, or notify FDA that you do not believe a labeling change is warranted, and submit a statement detailing the reasons why such a change is not warranted.

The labeling supplement should contain the Medication Guide for Botox/ Botox Cosmetic (botulinum toxin Type A). Include labeling in both Microsoft Word format and content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at: http://www.fda.gov/oc/datacouncil/spl.html.

Use the following designators to prominently label all submissions, including supplements, relating to this safety label change as appropriate:

SAFETY LABELING CHANGES UNDER 505(o)(4)-PRIOR APPROVAL SUPPLEMENT

OR
SAFETY LABELING CHANGES UNDER 505(o)(4)- CHANGE NOT WARRANTED

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

In accordance with section 505-1(a) of the FDCA, we have determined that a REMS is necessary for Botox/Botox Cosmetic (botulinum toxin type A) to ensure that the benefits of the drug outweigh the risks including the serious risk of distant spread of botulinum toxin effects after local injection and the potential serious risk of medication errors related to the lack of interchangeability of Botox/Botox Cosmetic (botulinum toxin type A) with other licensed botulinum toxin products.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Botox/Botox Cosmetic (botulinum toxin type A) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Botox/Botox Cosmetic (botulinum toxin type A). FDA has determined that Botox/Botox Cosmetic (botulinum toxin type A) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use, Botox/Botox Cosmetic (botulinum toxin type A). FDA has also determined that Botox/Botox Cosmetic (botulinum toxin type A) is a product for which patient labeling could help prevent the consequences of serious adverse events. Under 21 CFR 208 you are responsible for ensuring that the Medication Guide is available for distribution to patients who receive Botox/Botox Cosmetic (botulinum toxin type A) injections.

The Medication Guide submitted as a safety labeling change, noted above, will be considered part of the REMS in accordance with 505-1(a).

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe and/or inject Botox/Botox Cosmetic (botulinum toxin type A) will support implementation of the elements of your REMS. The communication plan must provide for the dissemination of information about Botox/Botox Cosmetic (botulinum toxin type A), and information about the serious product risks including potential distant spread of botulinum toxin effects after local injection, and information about the lack of interchangeability of Botox/Botox Cosmetic (botulinum toxin type A) with other licensed botulinum toxin products.

The communication plan must include, at minimum, the following:

a. Dear Healthcare Provider Letters to be distributed with the approval of the Botox/Botox Cosmetic (botulinum toxin type A) labeling and Medication Guide to neurologists, dermatologists, and other specialists and healthcare professional staff who prescribe or inject Botox/Botox Cosmetic (botulinum toxin type A) or other botulinum toxin products.
b. Information pertaining to lack of interchangeability of Botox/Botox Cosmetic with other licensed botulinum products.
c. A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to whom the communication materials will be directed. This should be inclusive of all Botox /Botox Cosmetic (botulinum toxin type A) prescribers.
d. A schedule for when and how these letters/materials are to be distributed to healthcare providers.

Timetable for Submission of Assessments: The proposed REMS must include a timetable for submission of assessments that shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the

assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Each assessment must assess the extent to which the elements to assure safe use of your REMS are meeting the goals of your REMS and whether the goals or elements should be modified.

In accordance with section 505-1, within 30 days of the date of this letter, you must submit a prior-approval supplement containing your proposed REMS.

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information about Botox/Botox Cosmetic (botulinum toxin type A) (see Appendix A). Include information in the template that is specific to your proposed REMS for Botox/Botox Cosmetic (botulinum toxin type A). Additionally, all relevant proposed REMS materials, including the draft communication plan letters and other educational materials, should be appended to the proposed REMS. Once FDA finds the content acceptable, we will include this document as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

The REMS supporting document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but may not be limited to:

1. A survey of patients' understanding of the serious risks of Botox/Botox Cosmetic (botulinum toxin type A).

2. A survey of prescribers' understanding of the serious risks of Botox/Botox Cosmetic (botulinum toxin type A) and the lack of interchangeability of Botox/Botox Cosmetic (botulinum toxin type A) units with those of other licensed botulinum toxin products.

3. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24.

4. A report on failures to adhere to distribution and dispensing requirements, and corrective actions to address non-compliance.

5. An assessment of use data including:
   a. extent of use (denominator estimates)
   b. number of patients by age

6. A summary of reports of all potential or diagnosed cases of distant spread of botulinum toxin effects after local injection with Botox/Botox Cosmetic (botulinum toxin type A).

7. A summary of reports of all medication errors involving interchangeability of Botox/Botox Cosmetic (botulinum toxin type A) units with those of other licensed botulinum toxin products.

Prominently identify proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission:

NEW SUPPLEMENT FOR BLA 103000
PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

SUPPLEMENT [assigned #]
PROPOSED REMS - AMENDMENT

If you do not submit electronically, please send 5 copies of your REMS-related submissions.

POSTMARKETING REQUIREMENTS UNDER 505(o)

In accordance with section 505(o)(3) of the FDCA, we have determined, based on new safety information, that you should be required to conduct certain postmarketing studies and trials. In addition to the new safety information described above, since the approval of Botox/Botox Cosmetic (botulinum toxin type A), based on botulinum toxin product clinical trial data, we have become aware of unexpected serious risks related to postnatal growth and development and signals of serious risks related to the effects on blood glucose and alkaline phosphatase as a marker of bone metabolism.
We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the unexpected serious risk of adverse effects on postnatal growth and development.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to identify this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following:

1. A juvenile rat toxicology study is required to identify the unexpected serious risk of adverse effects of Botox (botulinum toxin type A) on postnatal growth and development. The study should utilize animals of an age range and stage(s) of development that are comparable to the intended pediatric population; the duration of dosing should cover the intended length of treatment in the pediatric population. In addition to the usual toxicological parameters, this study should evaluate effects of Botox (botulinum toxin

type A) on growth, reproductive development, and neurological and neurobehavioral development.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of serious risk related to the distant spread of toxin effects in pediatric and adult patients with spasticity treated with Botox (botulinum toxin type A) and signals of serious risks related to the effects on blood glucose and alkaline phosphatase as a marker of bone metabolism.

2. (b) (4)

Submit timetables for final protocol submission, trial completion, and submission of the final report for the postmarketing requirements described above by 30 days from the date of this letter.

Submit the protocols to your IND, with a cross-reference letter to BLA 103000. Submit all final reports to your BLA 103000. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

- **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o)**
- **REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o)**
- **REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii), provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70

We request your agreement to conduct the following postmarketing commitments:

(b) (4)

Submit timetables for final protocol submission, trial completion, and submission of the final report for the postmarketing commitments described above by 30 days from the date of this letter.

We acknowledge that you have submitted an efficacy supplement for the treatment of upper extremity spasticity in adults. The trials submitted in that efficacy supplement are under review, and FDA will determine whether these trials are adequate to fulfill any part of this commitment.

We request that you submit clinical protocols to your IND, with a cross-reference letter to BLA 103000. Submit all final reports to your BLA 103000. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **Postmarketing Commitment Protocol**
- **Postmarketing Commitment - Final Study Report**
- **Postmarketing Commitment Correspondence**
- **Annual Status Report of Postmarketing Commitments**

For each postmarketing commitment subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing commitments for this product. The status report for each commitment should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer

to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm for further information).

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Tamy Kim, PharmD, Safety Regulatory Project Manager, at (301) 796-1125.

Sincerely,

Dr Norman Haughawout signing
for Dr. Russell Katz

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Tatiana Oussova, MD
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Draft Medication Guide
Appendix A REMS Template
Appendix B REMS Supporting Document Template

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix A: REMS Template

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Appendix B: supporting document

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Assessment of the REMS (for products approved under an NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information