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Evaluation of the Safety and Effectiveness of BOTOX® (Clostridium Botulinum Toxin Type A) in the Treatment of Patients with Urinary Incontinence due to Neurogenic Detrusor Overactivity or Overactive Bladder: A Post-marketing Surveillance Study in Korea

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Approval Date: 04-Nov-2013

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1. Study Drug and Indication

1.1 Study Drug

BOTOX® (Clostridium Botulinum Toxin Type A) Purified Neurotoxin Complex (US Adopted Name is onabotulinumtoxinA), henceforth referred to as BOTOX

1.2 Target Indication

The treatment of urinary incontinence due to neurogenic detrusor overactivity (NDO), e.g., spinal cord injury (SCI) or multiple sclerosis (MS), or overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency in adults ≥ 18 years of age who have an inadequate response to or are intolerant of an anticholinergic medication.

2. Study Title

Evaluation of the safety and effectiveness of BOTOX in the treatment of patients with urinary incontinence due to NDO or OAB: a post-marketing surveillance (PMS) study in Korea

3. Study Objectives

The purpose of this PMS study is to evaluate the safety and effectiveness of BOTOX for the treatment of patients with urinary incontinence due to either NDO or OAB through active surveillance under routine clinical practice after the launch of BOTOX in Korea.

The specific aims are to report on the:

(1) Safety of BOTOX treatment in patients with NDO or OAB by describing and quantifying the adverse events (AEs) experienced by patients with NDO or OAB treated with BOTOX. AEs will be summarized by serious adverse events (SAEs), non-SAEs, known adverse drug reactions (ADRs) per Korean prescribing information, and unexpected AEs. Incidence rates of these AEs will also be calculated.

(2) Effectiveness of BOTOX in treating patients with NDO or OAB as measured by the change in ICIQ-SF scores after BOTOX treatment from baseline (ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form).

4. Study Design

4.1 Study Population

Adult patients (≥ 18 years of age) with urinary incontinence due to NDO, e.g., as a result of SCI or MS, or with symptoms of urge urinary incontinence, urgency, and frequency due to OAB who have an inadequate response to or are intolerant of an anticholinergic medication as evaluated and determined by treating physicians

4.2 Planned Surveillance Sites

BOTOX in the treatment of NDO or OAB is expected to be mainly used in hospitals/clinics with urology and/or urogynecology departments. Therefore, this surveillance will be mainly conducted by collecting relevant information on treated patients from contracted specialists in the applicable departments in university hospitals, general hospitals, and hospitals/clinics.

4.3 Site/Physician Recruitment

Only sites that have investigators treating eligible patients with BOTOX, that are capable of following local and national regulations on Human Subject Protection, and that agree to participate in this PMS study will be selected.

The sponsor will contract with the relevant hospitals (department or physician) to collect post-marketing data on the use of BOTOX for the treatment of NDO or OAB.

The active surveillance study will begin after a contract has been executed between the hospital/principal investigator and Allergan. In the event that a contracted principal investigator is changed during the agreed surveillance period, a replacement (e.g., co-investigator) will be identified to assume the role of principal investigator to ensure continuity of the surveillance study. For this purpose, a separate contract or an amendment to the contract will be executed with the new principal investigator and the regulatory authority will be notified of changes.

4.4 Patient Recruitment

The investigators will continuously enroll all eligible patients treated with BOTOX at the relevant hospital(s) to ensure unbiased enrollment of patients during the agreed surveillance period. Only those patients who have consented to the study by signed Informed Consent Form (ICF) will be included in the study. The decision to treat a patient with BOTOX is determined by the physician and patient, and is separate from the decision to include the

patient in the study. Participation in the study (or lack thereof) will in no way influence the patient's eligibility to be treated with BOTOX.

4.5 Study Size

In compliance with Article 6.3, which is the standard on the re-evaluation of new medicines (Notification No. 2011-60 of the Korea Ministry of Food and Drug Safety [MFDS], 10 October 2011), Allergan plans to study approximately 600 patients with NDO or OAB who have received BOTOX injection(s) for the treatment of urinary incontinence and other symptoms.

4.6 Data Source and Collection

4.6.1 Data Source

The investigator or his/her designee will collect the required information on enrolled patients utilizing Allergan-provided electronic case report forms (eCRFs). Paper CRFs will also be available in the event the EDC system becomes temporarily inaccessible. However, all paper CRFs will be entered into the EDC system by the study site within 3 months of the follow-up visit or before database lock.

For this non-interventional surveillance study, the visit schedule is determined by the physician based on clinical judgment and patient preference, and not determined a priori by the study design.

Investigators will collect safety and effectiveness data at the first follow-up visit during the period from 1 month to 4 months after BOTOX treatment. Data will be collected by interviewing patients and/or reviewing medical charts. If a patient has not scheduled a follow-up visit within 4 months after BOTOX treatment, investigator or his/her designee will contact the patient by telephone to collect follow-up safety and effectiveness information. If a patient cannot be reached or does not wish to answer questions, this patient will be considered as a loss of follow-up and the reason will be recorded.

Investigators will be trained to report AEs and SAEs according to Allergan's AE reporting policy to ensure there are no delays in reporting AEs/SAEs to either Allergan's Pharmacovigilance Team or Health Authorities in accordance with local regulatory requirements.

4.6.2 Data Items on Case Report Forms

4.6.2.1 Basic Information

- CRF Number
- Investigating physician information:
  - Site name
  - Site number
  - Department name
  - Physician's name
- Patient information
  - Patient initials
  - Patient's unique study identification number
- Date of initial visit
- Date and type of follow-up visit (i.e., in-office, phone call, loss of follow-up)
- If loss of follow-up, specify reason

4.6.2.2 Patient Background Information and Medical History

- Sex
- Age
- Height/weight
- Treatment setting (i.e., outpatient, inpatient)
- History of allergies
- Pregnancy status (for female patients)
- Renal or hepatic impairment (Yes/No)
- Diagnosis of NDO or OAB

- Date urinary incontinence was first diagnosed
- Previous anticholinergic therapy and reason(s) patient was inadequately managed by anticholinergic therapy
- For OAB patients, was another OAB drug also used (e.g. beta 3 agonist) after anticholinergic therapy? If yes, please specify Name of Drug/ start/ stop date Previous use of sacral neuromodulation therapy
- For patients with NDO: Underlying neurologic condition (Yes/No; if yes, specify MS, SCI, or other), duration of underlying neurologic condition, and duration since NDO diagnosis
- For patients with OAB: Time since diagnosis of OAB
- Urinary catheterization on a regular basis prior to BOTOX injection, and post void residual (PVR) urine volume if patient is not routinely using catheterization
- Past BOTOX or other Botulinum Toxin use and indications
- Other medical history (complications of underlying diseases, concurrent disease, and surgeries, e.g., bladder sling)

4.6.2.3 Laboratory Tests

- Whether laboratory tests was done/available before and/or after BOTOX treatment
- Date laboratory test was done and results
- Any change after BOTOX treatment
- Whether or not the laboratory test result was reported as an adverse event

4.6.2.4 Concomitant Medications

Concomitant medications administered with BOTOX will be recorded. Items for evaluating concomitant medications are as follows:

- Whether other medications were concomitantly administered or used
- Drug name (generic name; for Botulinum Toxin, specify trade name)
- Route of administration

- Frequency
- Dosage
- Treatment duration: start date, end date
- Reason/Indication for drug use

4.6.2.5 Information Related to BOTOX Injection

A. Injection of BOTOX for NDO or OAB

- Treatment date
- Number of injection sites in the bladder
- Total dosage injected into the bladder

B. Anesthesia

- Whether BOTOX injection was done under local or general anesthesia

C. Prophylactic Antibiotic Use

- Whether antibiotic prophylaxis was used prior, during, or after BOTOX injection procedure
- Type of antibiotic prophylaxis used, route of administration, frequency, dosage, start and stop dates

D. Catheterization information

- Catheterization after BOTOX administration (Yes/No)
- If catheterizing, reason for catheterization
- If catheterizing was due to urinary retention after BOTOX administration, specify PVR urine volume before catheterization
- Duration of catheterization: start date, stop date

4.6.2.6 Safety Variables

All AEs that occur during BOTOX administration and/or after BOTOX administration during the follow-up period will be collected regardless of causal relationship to BOTOX. The safety assessment will include all undesirable changes of medical findings (including laboratory test findings) and all AEs associated with BOTOX injection.

Pregnancy status (for female patients) will be requested during follow-up period; in the situation that the patient became aware of a pregnancy after the Botox administration. The patient will be asked to participate in Allergan's 'Pregnancy Exposure Surveillance' in order to analyze and evaluate the risk, if any, associated with the use of the Drug during pregnancy.

The following information will be collected for the surveillance of adverse events:

- Presence or absence of an adverse event
- Type of adverse event
- Start and stop date of adverse event
- Severity of adverse event
- Whether adverse event met criteria for serious event
- Category for serious adverse event
- Current status of adverse event
- Causal relationship to BOTOX, injection procedure, protocol-required activities, or concurrent medical conditions, etc.
- Change in BOTOX treatment after adverse event
- Any treatment given for the adverse event
- Physician's comments on reported AE

4.6.2.6.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily

have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Severity of Adverse Event

The severity of AEs will be determined according to the following criteria:

- Mild
  Event(s) showing subjective or objective symptoms but not interfering with the patient's daily activities; the continuous treatment of the drug is possible without changing its dosage.
- Moderate
  Symptom(s) interfering with the patient's daily activities; the dosage decrease or treatment is required due to adverse event(s).
- Severe
  Symptom(s) resulting in the patient's inability to undertake daily activities; the drug should be discontinued due to severity of the AE.

Serious Adverse Event

A serious adverse event (SAE) is any adverse event occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse event
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity, or
- a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Allergan considers all cancer adverse events as serious adverse events. In addition, Allergan considers any abortion (spontaneous or non-spontaneous) as a serious adverse event.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a patient requires hospitalization are not reportable as serious adverse events.

Causality of Adverse Event

Physician investigators will be trained to systematically assess the causal relationship of AEs using the following definitions to determine the relationship of the AE to BOTOX treatment. There are 2 concepts for determining causal relationship of an AE to BOTOX: the drug itself and the injection procedure. Decisive factors for the assessment of causal relationship of an AE to BOTOX include, but may not be limited to, temporal relationship between the AE and the BOTOX injection, known side effects of BOTOX, medical history, concomitant medication, and course of the underlying disease.

Per MFDS's Guideline for PMS, the following definitions will be used to assess causation:

- Certain

  Considering timing of medication administered and onset of an AE, there is a reasonable relationship between the AE and surveillance medication. The AE cannot be explained by other concurrent medication, chemicals or other underlying disease. There is clinically reasonable response to withdrawal of the drug. The same event recurred following rechallenge with the same drug alone.

- Probable/likely

  Considering timing of medication administered and onset of an AE, there is a reasonable relationship between the AE and the surveillance drug. The AE does not appear to be related to concurrent medication, chemicals, or other underlying disease, and shows a clinically reasonable response on stopping the surveillance drug. (There is no information on re-challenge.)

- Possible

  Considering timing of medication administered and onset of an AE, there is a reasonable relationship between the AE and the surveillance drug. However, the AE can be also explained by other concurrent medication, chemicals, or underlying

disease. Information on response when stopping the surveillance drug is not sufficient or available.

- Unlikely

  It is a transient AE that is unlikely to be related to the surveillance drug based on the timing of medication and onset of the AE. The AE can be reasonably explained by other concurrent medication, chemicals or other underlying disease.

- Conditional/unclassified

  More data is required for appropriate evaluation or additional materials are being reviewed.

- Unassessable/unclassifiable

  Information is insufficient or contradictory to such an extent that a judgment cannot be made and it is not possible to supplement or confirm such information.

After determining the causal relationship of the AEs, the physician must report all AEs to Allergan or its representatives whether, according to the physician's judgment, the AE is "certainly or likely related to BOTOX". The investigators will receive training on the procedure for reporting AEs to Allergan or its representatives, including the requirement to notify Allergan immediately, but no later than 24 hours, after learning of all SAEs identified during the study.

Pregnancy

Pregnancy is defined as the use of Allergan Product during pregnancy or coincident with conception.

4.6.2.7 Effectiveness Variables

The International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) instrument will be used to evaluate effectiveness. The ICIQ-SF will be administered to patients before the injection of BOTOX and at the next office visit within 1 to 4 months after injection of BOTOX. The pre-injection and post-injection dates of completion of the ICIQ-SF will be recorded. The total ICIQ score is the sum of values from the first 3 questions below.

The International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF)

Questions	Scale
How often do you leak urine?	0 Never 1 About once a week 2 Two or three times a week 3 About once a day 4 Several times a day 5 All the time
How much urine do you usually leak (whether you wear protection or not)?	0 None 2 A small amount 4 a moderate amount 6 A large amount
Overall, how much does leaking urine interfere with your everyday life?	0(Not at all) --- --- --- --- --- --- ---10 (A great deal) 0 1 2 3 4 5 6 7 8 9 10
When does urine leak? (Please check all that apply to you.)	Never-urine does not leak Leaks before you can get to the toilet Leaks when you cough or sneeze Leaks when you are asleep Leaks when you are physically active/exercising Leaks when you have finished urinating and are dressed Leaks for no obvious reason Leaks all the time

The evaluation will be based on the change in the total score before and after administration of the BOTOX (ICIQ Score change = post-injection ICIQ score – pre-injection ICIQ score).

If the ICIQ-SF is not completed for either baseline (pre-injection) or after BOTOX treatment (post-injection), investigators will be asked to provide the reason why the form was not completed and comment on the patient's general condition before and after BOTOX treatment.

4.7 Study Duration

The BOTOX NDO indication was approved on 30 August 2012 in South Korea. Per MFDA PMS guidelines, the study should be completed within 4 years after the approval date, i.e., by

30 August 2016. The PMS protocol for BOTOX NDO was approved by MFDA in May 2013. Therefore, the study duration is from May 2013 to August 2016.

The OAB indication was approved on 18 October 2013 in South Korea and the original PMS protocol for BOTOX NDO herein to be amended to include OAB indication. The recruitment of OAB patients will start after this protocol amendment is approved by MFDS. The overall BOTOX NDO/OAB PMS study duration will remain the same as originally determined for BOTOX NDO PMS, i.e. from May 2013 to August 2016.

4.8 Data Management and Retention

An electronic data collection (EDC) system will be used to record all information in the study. Only de-identified data on these patients will be captured and used in study analyses. Allergan or its representative will provide training on the study procedures, completing eCRFs, and AE reporting requirements.

The documents prepared during this study, including records on the post-marketing surveillance, database, study protocol, investigator contract, and eCRFs will be filed promptly after receipt by Allergan and retained for 3 years after completion and submission of the surveillance report.

4.9 Data Analysis Variables and Analysis Methods

4.9.1 Analysis Variables

4.9.1.1 Composition of Patients

Tables showing the composition of the surveillance patients will be generated. The following information will be provided:

- Number of patients enrolled
- Number of patients who dropped out and reasons for dropout
- Number of patients with CRFs: the number of patients whose CRFs were collected
- Number of patients for safety assessment: the number of patients who met the safety evaluation selection criteria
- Number of patients for effectiveness assessment: the number of patients who met the effectiveness evaluation selection criteria

Patients will be included in the analysis to determine the safety and effectiveness of BOTOX if they meet the following criteria:

A. Inclusion criteria for safety assessment

- Patients who were treated with BOTOX and whose safety data were collected

B. Inclusion criteria for effectiveness assessment

- Patients who were treated with BOTOX and who were evaluated for effectiveness of BOTOX for the treatment of NDO or OAB based on the ICIQ-SF data and/or the judgment of the participating treating physician
- The final valid cases for effectiveness evaluation include those patients who have completed both pre- and post-BOTOX injection effectiveness evaluations

4.9.2 Analysis Methods

The analyses will be descriptive in nature, and there are no plans for formal statistical hypothesis testing. Results will be displayed in tabular format (i.e., summary statistics, frequency distribution of item responses, and incidence rates with corresponding 95% confidence intervals [CI]). No imputations for missing data are planned.

A detailed Statistical Analysis Plan will be prepared prior to data analysis. The key elements of analysis are summarized in this section.

4.9.2.1 Descriptive Statistics

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. NDO and OAB patients will be analyzed together, as well as separately. Categorical variables (e.g., gender) will be summarized by the number and percentage (%) of patients in each category. Any missing category included in the CRF or generated from data collection will be treated as an independent category. For describing the incidence of adverse events, the frequency, cumulative incidence proportion, patient-year incidence rate, and 95% CI for the cumulative incidence measures will be displayed. Unless otherwise specified, the 95% CI of the proportions will be calculated using the exact method, and the 95% CI of the incidence rates will be constructed assuming the frequency of a particular event in a given period of time follows a Poisson distribution.

Continuous variables (e.g., age) will be summarized using descriptive statistics (number of non-missing values, mean, standard deviation, median, minimum and maximum values).

Additional exploratory descriptive and inferential analyses of the data will be conducted as deemed appropriate. This document will be updated only if these additional analyses change a principal feature of the analyses described here.

4.9.2.2 Safety Analysis Methods

A summary table of AE frequency by system organ class and preferred term will be generated for SAEs, non-SAEs, ADRs, unexpected ADRs. The severity, outcome, and causal relationship of the AE to BOTOX treatment (separately for BOTOX and BOTOX injection procedure), and whether or not treatment for the AE was given will also be described.

In addition, patient demographic and disease/treatment characteristics will be summarized in total patients, as well as by presence or absence of AE as appropriate.

The World Health Organization Adverse Reactions Terminology (WHOART) will be used in data reporting at the level of system organ class and preferred terms.

4.9.2.3 Effectiveness Analysis Methods

The change from the baseline value of the ICIQ-SF (before BOTOX injection) and after BOTOX injection (post ICIQ score – pre ICIQ score) will be calculated for each patient (ICIQ-SF change).

Mean, standard deviation, median, and ranges for ICIQ-SF change will be calculated. In addition, a frequency table will be generated for the amount of ICIQ-SF change. Stratified analysis by subgroups, e.g. NDO, OAB, underlying diseases, etc. will be performed as appropriate.

5. Others

5.1 Protocol Amendment

When a significant change in administration, dosage, indications, or study conduct is required or anticipated during the active surveillance period of BOTOX for the treatment of NDO or OAB, the protocol will be amended accordingly and submitted to MFDS.

5.2 Actions to be Taken When Problems and Questions are Identified

If unexpected adverse drug reactions or SAEs occur, or in the event that the incidence of AEs significantly increases, or safety and effectiveness issues not observed prior to marketing are observed, efforts will be made to investigate such observations in order to verify their significance.

In addition, if unusual trends or changes associated with safety are observed during the conduct of this surveillance study, or in reports such as the spontaneous reporting of adverse events, special attention will be paid to examine such trends or safety changes using data obtained from the surveillance study. During this re-evaluation period of BOTOX in NDO or OAB, the active surveillance study will provide the opportunity to identify unexpected adverse reactions which were not observed during the BOTOX NDO and OAB clinical development programs and potentially substantiate the very rare adverse events for which no causal relationship with BOTOX has been established.

5.3 Reporting of Adverse Events and Pregnancy

Information regarding all adverse events that occurred following administration of BOTOX for the treatment of NDO or OAB regardless of causality to the surveillance drug, including start and stop dates, severity, causality to the study drug, actions taken, outcome, and any other medically relevant information that may be necessary to fully understand the course of event(s) will be recorded in the corresponding section in the CRF. A safety management plan, describing roles, responsibilities, and timelines for identifying, collecting, and reporting of adverse event data to Allergan Safety Information Management and Reporting (SIMR) and Health Authorities as required, will be developed to train investigators on reporting AEs and SAEs.

In the event of an SAE, the investigator must:

1. Notify Allergan or its representatives immediately, but no later than 24 hours by online eCRF. In the situation that the eCRF cannot be completed in a timely manner or in case of the EDC system is temporarily not accessible, fax or email the paper CRF (contact details can be found on page 1) can be used to report SAEs within 24 hours. Emergency phone numbers and relevant Allergan personnel contacts are also on the front page of the protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.

3. Provide Allergan with a complete, written description of the adverse event(s) on the CRF describing the event chronologically, including any treatment given (e.g., medications administered, procedures performed) for the adverse event(s). Summarize relevant clinical information about the event: signs, symptoms, diagnosis, clinical course and relevant clinical laboratory tests, and any other medically relevant information that may be necessary to fully understand the course of event(s). Include any additional or alternative explanation(s) for the causality which includes a statement as to whether the event was or was not related to the use of the investigational drug.

4. Promptly inform the governing IEC of the serious adverse event as required by the IEC, local regulations, and the governing health authorities.

In the event of a pregnancy, the investigator must:

1. Notify Allergan or its representatives immediately via email or telephone, but no later than 24 hours after becoming aware of the pregnancy

2. Obtain the patient's approval to participate in Allergan's 'Pregnancy Exposure Surveillance'

3. Further handling and Follow up activities in case of pregnancy is described in the Safety Management Plan (SMP).

5.4 Human Subject Protection

IEC approval consistent with local regulations will be obtained for each site. Prior to enrollment of patients at a given site, the study protocol will be submitted together with its associated documents (e.g., ICF, CRF, and communication materials) to the responsible IEC for its review. The approval of the IEC will be filed in the Contract Research Organization's (CRO's) Study Master File. Patient enrollment will not start at any site before the approval from the concerned IEC. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data by local laws and regulations. In database and reports, each patient will be unambiguously identified by a study ID, which links all the data reported for that specific patient.

5.5 Reporting and Dissemination of Results

In compliance with Korea MFDS requirements, results of the PMS study will be summarized and reported to MFDS periodically according to the following schedule: every 6 months for the first 2 years and annually for the remaining 2 years. Each report will be submitted within 2 months of the end of each reporting period.. At the end of the surveillance period (4 years post-approval date), a final report will be prepared and submitted to MFDS.

6. Appendices

6.1 Case Report Form (attached)

6.2 BOTOX® Summary of Product Characteristics

6.3 Glossary of Abbreviations

Term/Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
CI	confidence interval
CRF	case report form
CRO	Contract Research Organization
GCP	Good Clinical Practices
ICIQ-SF	International Consultation on Incontinence Questionnaire Short Form
ICF	informed consent form
IEC	Independent Ethics Committee
MFDS	Ministry of Food and Drug Safety
MS	multiple sclerosis
NDO	neurogenic detrusor overactivity
OAB	overactive bladder
PMS	post-marketing surveillance
PVR	post void residual
SAE	serious adverse event
SCI	spinal cord injury
SIMR	Safety Information Management and Reporting
WHOART	World Health Organization Adverse Reactions Terminology

6.4 Protocol Amendment 1 Summary

Title: Evaluation of the Safety and Effectiveness of BOTOX® (Botulinum Toxin Type A) in the Treatment of Patients with Urinary Incontinence due to Neurogenic Detrusor Overactivity or Overactive Bladder: A Post-Marketing Surveillance Study in Korea

Protocol 191622-134, Amendment 1

Date of Amendment: October 2013

Amendment Summary

This summary includes changes made to Protocol 191622-134 Amendment 1. This protocol was amended to add the target indication of overactive bladder.

Following is a summary of content-oriented changes that were made to each section of the protocol, and a brief rationale for these changes. Minor editorial and document formatting revisions have not been summarized.

Section(s)	Revision	Rationale
Title page, 1.2, 2, 3, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6.2, 4.7, 4.9, 5.1, 5.2, 5.3	Added overactive bladder (OAB) as an additional target indication for BOTOX	MFDS approval of BOTOX for the OAB indication in Korea
4.6.1, 5.2, 5.3	Stated "electronic" case report form (eCRF)	Clarification
4.7	Added OAB approval date and clarified study duration period	Clarification due to addition of OAB indication
5.3	Bullet #4: Removed "IRB"	Not relevant to this study
	Added process of reporting pregnancy	Required by Allergan AE reporting standard
5.5	Changed "KFDA" to "MFDS" throughout the document	Correction

CRF Number	

BOTOX® Post-Marketing Surveillance Study CRF

Urinary Incontinence due to Neurogenic Detrusor Overactivity or Overactive Bladder

Name of Research institution		**Name of Reporting Physician**	
Site Number		**Patient Initials (eg : HGD)**	
Department		**Patient Study ID**	
Date of Initial Visit (y/m/d)			

Date of Follow-up (y/m/d)	

Type of Follow-up

☐ **In-Office**

☐ **Phone Call (safety and effectiveness data collected via phone call)**

☐ **Loss of Follow-UP, reason (eg. Could not be reached, not willing to answer questions, etc.):**

_____

1. Patient Background Information

Sex ☐ Male ☐ Female	**Age** _____ Years Patient < 18 yrs old not eligible	**Height** _____ cm	**Weight** _____ kg
Treatment Setting	☐ Outpatient ☐ Inpatient	**History of Allergies**	☐ None ☐ Yes (Substances Allergic to):
Currently pregnant (if applicable)	☐ No ☐ Yes, if yes, which trimester? ☐ 1st ☐ 2nd ☐ 3rd ☐ unsure		
Renal Impairment	☐ No ☐ Yes	**Hepatic Impairment**	☐ No ☐ Yes
Diagnosis: Urinary incontinence is due to (circle one): ☐ **Neurogenic Detrusor Overactivity (NDO)**	**For patients with NDO:** Underlying neurologic condition: ☐Multiple Sclerosis Number of Years since Diagnosis: _____ ☐ Spinal Cord Injury Number of Years since Diagnosis: _____ ☐ Other, specify _____ Number of Years since Diagnosis: _____ **Duration since NDO Diagnosis:** ____Years		
☐ **Overactive Bladder (OAB)**	**For patients with OAB: Duration since OAB Diagnosis** _____ Years		
Date Urinary Incontinence was First Diagnosed: Year Month Day			
Routine Urinary Catheterization (before BOTOX)	☐ No ☐ Yes If No, most recent Post-Void Residual Urine volume (mL) _____ Date of most recent PVR measurement (y/m/d): _____		

Previous Anticholinergic Therapy	Name of drug(s) (list below)	Start Date (y/m/d)	Stop Date(y/m/d)
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
	Reason(s) patient was inadequately managed by anticholinergic therapy (check all that apply) □ Inadequate response to anticholinergic medication □ Intolerant to anticholinergic medication □ Other (Please specify)_____		
For OAB patients, was another OAB drug also used (e.g. beta 3 agonist) after anticholinergic therapy? If yes, please specify	Name of drug(s) (list below)	Start Date (y/m/d)	Stop Date(y/m/d)
	_____	_____	_____
	_____	_____	_____
	_____	_____	_____
Previous Use of Sacral Neuromodulation Therapy	□ No □ Yes If yes, Start Date: Stop Date:		

2. Previous BOTOX or Other Botulinum Toxin Treatment by Any Medical Specialist

□ **None**

□ **Yes**

If Yes, please specify type of Botulinum Toxin (provide Trade Name) _____

□ Focal muscle spasticity: # of injections: ___ Last injection date: ____

□ Detrusor overactivity : # of injections: ___ Last injection date: ____

□ Glabellar lines: # of injections: ___ Last injection date: ____

□ Cervical dystonia: # of injections: ___ Last injection date: ____

□ Chronic migraine: # of injections: ___ Last injection date: ____

□ Other therapeutics (eg. Strabismus, blepharospasm, or hyperhidrosis):
# of injections: ___ Last injection date: _____

□ Others; specify # of injections: ___ Last injection date: ___

3. **Medical History, Including Surgeries and Complications of Underlying Diseases**

□ None □ Yes (Please note below) □ Unknown

Disease/Surgery/Complications (e.g. hypertension, diabetes, coronary artery disease, hepatitis, bladder sling surgery, UTI, etc.)	**Occurred in the Past or Current ? (if dates are known, please enter)**	**Comment**
1)	start (y/m): __/__ end (y/m): __/__ Ongoing at the time of Botox treatment: yes/ No	
2)	start (y/m): __/__ end (y/m): __/__ Ongoing at the time of Botox treatment: yes/ No	
3)	start (y/m): __/__ end (y/m): __/__ Ongoing at the time of Botox treatment: yes/ No	
4)	start (y/m): __/__ end (y/m): __/__ Ongoing at the time of Botox treatment: yes/ No	
5)	start (y/m): __/__ end (y/m): __/__ Ongoing at the time of Botox treatment: yes/ No	

4. Laboratory Tests

Please indicate whether a lab test result is available before and/or after BOTOX treatment below

Lab Test Name	**Before BOTOX Treatment**			**After BOTOX Treatment**			As compared to before BOTOX treatment, has the lab test value changed?	**Report as Adverse Event**
	Lab test available Y/N	**Date of Test (y/m/d)**	**Result of Test**	**Lab test available Y/N**	**Date of Test (y/m/d)**	**Result of Test**		
1)BUN (mg/dl)							□ No □ Yes	□ No □ Yes
2)Cr (mg/dl)							□ No □ Yes	□ No □ Yes
3)Urine WBC (/HPF)							□ No □ Yes	□ No □ Yes
4)Urine RBC (/HPF)							□ No □ Yes	□ No □ Yes
5)Other: specify							□ No □ Yes	□ No □ Yes
6)Other: specify							□ No □ Yes	□ No □ Yes
7)Other: specify							□ No	□ No

							□ Yes	□ Yes

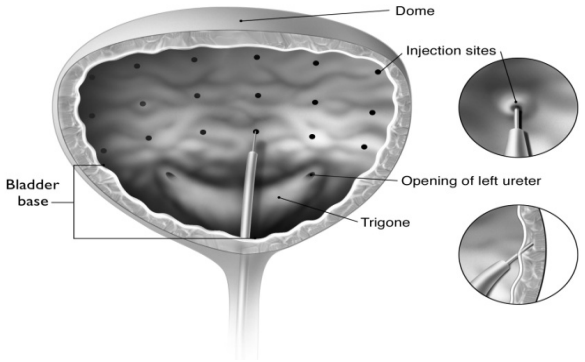
5. Concomitant Medication, including BOTOX® or other Botulinum Toxin used for non-urologic indications (please specify by trade names) prescribed by any medical specialist.

□ None □ Yes (Please record all medications that the patient is currently taking below)

Medical Name (Generic Name)/Botulinum Toxin (Trade name)	Route of Administration	Frequency	Dosage	Date Started (y/m/d)	Date Stopped (y/m/d)	Reason/ Indication
1)						
2)						
3)						
4)						
5)						
6)						
7)						
8)						
9)						

6. Information on Botox Injection*

Date of Injection (y/m/d)	# of Injection Sites	Total Units Injected	Anesthesia
/ /	□ 20 □ 30 or □ Other, specify _____	U	□None □Local □General



Approved total dose for overactive bladder is 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor

Approved total dose for neurogenic detrusor overactivity associated with a neurologic condition is 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor

*If there is any complication during the procedure, the complication should be considered as AE and recorded in the section below and complete the Non-Interventional Study AE Form.

7. Prophylactic Antibiotic Use

Was patient given antibiotics before, during, or after BOTOX treatment for prophylactic reason?

□ **No** □ **Yes**

If yes, please provide the following:

Generic Name of Antibiotics	Route of Administration	Frequency	Dosage	Date Started (y/m/d)	Date Stopped (y/m/d)
1)					
2)					

8. Catheterization After Botox Injection □ No □ Yes (If yes, please provide information in table below)

Reasons for Catheterization	If catheterization due to Urinary Retention, provide Post Void Residual Urine Value (ml) before catheterization, if Other, specify.	Duration of Catheterization Start to Stop Date (y/m/d)	
□ Urinary Retention □ Others, specify _____		/ / to / /	□ Ongoing

9. Evaluation of Effectiveness Before and After BOTOX Treatment

International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF)	**Before BOTOX Treatment (baseline)**	**After BOTOX Treatment (follow-up)**
	Completed By: _____ (initial / date)	Completed By: _____ (initial / date)
1. How often do you leak urine?	0 Never 1 About once a week 2 Two or three times a week 3 About once a day 4 Several times a day 5 All the time	0 Never 1 About once a week 2 Two or three times a week 3 About once a day 4 Several times a day 5 All the time
2. How much urine do you usually leak (whether you protection or not)?	0 None 2 A small amount 4 A moderate amount 6 A large amount	0 None 2 A small amount 4 A moderate amount 6 A large amount
3. Overall, how much does leaking urine interfere with your everyday like?	0(Not at all) ------- 10 (A great deal) 0 1 2 3 4 5 6 7 8 9 10	0(Not at all) ------- 10 (A great deal) 0 1 2 3 4 5 6 7 8 9 10
ICIQ Score	Sum 1+ 2+ 3 above	Sum 1+ 2+ 3 above
When does urine leak? (Please check all that apply to you).	□ Never- urine does not leak □ Leaks before you can get to the toilet □ Leaks when you cough or sneeze □ Leaks when you are asleep □ Leaks when are physically active/exercising □ Leaks when you have finished urinating and are dressed □ Leaks for no obvious reason □ Leaks all the time	□ Never- urine does not leak □ Leaks before you can get to the toilet □ Leaks when you cough or sneeze □ Leaks when you are asleep □ Leaks when are physically active/exercising □ Leaks when you have finished urinating and are dressed □ Leaks for no obvious reason □ Leaks all the time
If ICIQ is not completed before or after BOTOX treatment, please provide reason and impression of patient general condition		

10. Adverse Event

Adverse Event	Event 1
Adverse event description **(***diagnosis***)**	
Was the event onset after the subject exited the study? *If yes, provide details in Description of Event(s)*	☐ Yes ☐ No
Onset of event	/ /
Stop date *(date event resolved), if applicable*	/ /
Severity of symptoms (*select one)*	
Mild symptoms: symptoms not interfering with the patient's activities; the continuous treatment of the drug is possible without changing its dosage	☐
Moderate: symptoms interfering with the patient's daily activities; the dosage decrease or treatment is required due to AE	☐
Severe: symptoms resulting in the patient's inability to undertake daily activities; the drug should be discontinued due to severity of the AE	☐
Was the event serious*?	☐ Yes ☐ No
Seriousness criteria (if yes, *select all that apply)*	
Results in death	☐
Life-threatening	☐
Results in persistent or significant disability/incapacity	☐
Requires inpatient hospitalization or prolongs existing hospitalization	☐
Congenital anomaly/birth defect	☐
Other important medical event (*describe in Description of Event(s))*	☐
Current Status of Adverse Event (*select one)*	
Ongoing	☐
Resolved without sequelae	☐
Resolved with sequelae (*describe in Description of Event(s)*)	☐
Death (*describe in Description of Event(s)*)	☐
If subject died, enter date of death (DD/MMM/YYYY): / /	
Was an autopsy performed? ☐ Yes ☐ No ☐ Unknown	

Causal Relationship: Additional or alternative explanation(s) for the causality of the event may be selected (*provide details in the Description of Event(s) in Physician's Comments Section)*	
Is there a reasonable possibility that the event may have been caused by (*select all that apply***):**	
BOTOX	☐Certain ☐Probable/likely ☐Possible ☐Unlikely ☐Conditional/unclassified ☐Unaccessable/unclassibiable
BOTOX injection procedure?	☐Certain ☐Probable/likely ☐Possible ☐Unlikely ☐Conditional/unclassified ☐Unaccessable/unclassibiable
Protocol-required activities	☐ Yes ☐ No
Current Medical condition(s)	☐ Yes ☐ No
Medical or surgical procedures	☐ Yes ☐ No
Other known or suspected cause	☐ Yes ☐ No,
Concomitant drug(s)	☐ Yes ☐ No

Change in BOTOX treatment after AE *(select one)*	
None	☐
Regimen changed	☐
Discontinued	☐
Not applicable	☐
Treatment Received for Adverse Event	☐ Yes ☐ No
If yes, what treatment, specify →	

Reporting Physician's Comments on reported AE:

∗ In the event of a serious adverse event, notify Allergan or its representatives immediately, but no later than 24 hours by completing online eCRF or fax (82-2-3019-4562) or email (sung_sukyoung@allergan.com) the paper CRF. By checking 'YES' for 'was event serious?' using online eCRF, an automatic alert will be sent immediately from the EDC system to Allergan PV mailbox.

Date of eCRF Entry	Year Month Date	Name of Reporting Physician	(e)Signature of Reporting Physician

ALLERGAN

Protocol 191622-134 Amd (Korea PMS) Final2NOV2013

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
04-Nov-2013 11:32 GMT-08	Haag-Molkenteller_Cornelia	Clinical Development Approval
04-Nov-2013 12:21 GMT-08	Kaplowitz_Haley	Management Approval