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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 Phase IV Non-interventional Post-marketing Surveillance Study in India

Protocol Number:	191622-140
Phase:	Phase IV Post-marketing Surveillance Study
Name of Investigational Product:	
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1. Study Drug and Indication

1.1 Study Drug

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

1.2 Target Indication

The treatment of adults ≥ 18 years of age with urinary incontinence due to neurogenic detrusor overactivity (NDO), eg, spinal cord injury (SCI) or multiple sclerosis (MS), or overactive bladder (OAB) 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 phase IV non-interventional post-marketing surveillance study in India

3. Study Objectives

The purpose of this phase IV post-marketing surveillance 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 India.

The specific aims are to report on the:

(1) Safety of BOTOX treatment in patients with NDO or OAB by identifying and evaluating adverse events (AEs) and rates of these events, including serious adverse events (SAEs) and non-serious AEs

(2) Effectiveness of BOTOX in treating patients with NDO or OAB using the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF)

4. Study Design

4.1 Study Population

Adult patients (≥ 18 years of age) with urinary incontinence due to NDO, eg, as a result of SCI or MS, or 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 departments in India. Therefore, this surveillance will be mainly conducted by collecting relevant information on treated patients from contracted specialists in the applicable departments in hospitals and 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 phase IV post-marketing surveillance 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 (eg, 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 (or lack thereof) in the study in no way would influence the patients eligibility to be treated with BOTOX.

4.5 Study Size

In compliance with the Conditions of Additional Indication NOC issued by the DCGI office dated 19 March 2013, Allergan plans to study approximately 250 patients with NDO or OAB who have received BOTOX injection(s) for the treatment of urinary incontinence.

4.6 Data Source and Collection

4.6.1 Data Source

The investigators will collect the required information on enrolled patients utilizing Allergan-provided case report forms (CRFs) once the contract has been executed.

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

Investigators will collect: (1) baseline and BOTOX treatment information at the initial visit when patients receive BOTOX treatment, and (2) safety and effectiveness data at the first follow-up visit during the period from 1 to 4 months after BOTOX treatment. If a patient has not scheduled a follow-up visit within 4 months after BOTOX treatment, investigator or his/her designate will contact patient by telephone to collect follow-up safety and effectiveness information. If a patient could not be reached or does not wish to answer questions, this patient will be considered to be a dropout. Data will be collected through patient interviews or medical record abstraction (eg, laboratory results).

Investigators will be trained to report AEs according to Allergan's AE reporting policy to ensure no delays in reporting AEs 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 Survey of Basic Information Before BOTOX Administration

A. Basic information

- CRF Number
- Investigating Physician Information:
  - Site name
  - Department name
  - Physician's name
- Patient's initials

B. Patient background information and medical history

- Gender
- Age
- Type of patient, ie, outpatient, inpatient
- Height/weight
- History of allergy
- Past BOTOX or other Botulinum Toxin use and indications
- Date of diagnosis/first occurrence of urinary incontinence
- Previous anticholinergic therapy and reason(s) patient was inadequately managed by anticholinergic therapy
- Previous use of sacral neuromodulation therapy
- Other medical history (complications, concurrent disease, and surgeries, eg, bladder sling)
- For patients with NDO: Underlying neurologic condition (Yes/No; if yes, specify MS, SCI, or other)
- For patients with NDO: Time since diagnosis of neurologic condition
- For patients with NDO: Urinary catheterization on a regular basis prior to BOTOX injection, and post void residual (PVR) urine volume if patient is not routinely using catheterization
- For patients with OAB: Time since diagnosis of OAB
- For female patients: Current pregnancy status

4.6.2.2 Current Treatment

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. Concomitant medications

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

- Whether antibiotic prophylaxis was used prior, during, or after BOTOX injection procedure
- Type of antibiotic prophylaxis used
- Duration of antibiotic prophylaxis
- Whether other medications were concomitantly administered or used
- Drug name (generic name; for Botulinum Toxin, specify trade name)
- Route of administration
- Treatment duration: start date, end date
- Frequency/dosage
- Indication for drug use

4.6.2.3 Survey of Information After BOTOX Administration

- Catheterization after BOTOX administration
- 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, end date

4.6.2.4 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 that is considered to be an AE

4.6.2.5 Safety Measures

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.

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

- Presence or absence of an adverse event
- Severity of adverse event
- Seriousness criteria met
- If AE is present, the following detailed information will be collected using the Non-interventional Study Adverse Event Form
  - Description of adverse event
  - Start and stop date of adverse event
  - For SAE, specific type, eg, death, hospitalization, etc.
  - Outcome of adverse event
  - Causal relationship to BOTOX
  - Action regarding BOTOX treatment
  - BOTOX injection date
  - Relevant medical history
  - Relevant concomitant medications

- Physician's comments on reported AE, including treatment given for AE

4.6.2.6 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 (including 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.

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.

Severity of Adverse Event

A clinical determination will be made of the intensity of an adverse event. The severity assessment for an AE must be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated.
Moderate	Discomfort enough to cause interference with usual activity.
Severe	Incapacitating with inability to work or do usual activity.
Not applicable	In some cases, an adverse event may be an 'all or nother' finding which cannot be graded.

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.

- **Not related:** Not suspected to be reasonably related to the BOTOX or injection procedure. The AE could not medically (pharmacologically/clinically) be attributed to BOTOX or injection procedure. A reasonable alternative explanation must be available.

- **Related:** Suspected to be reasonably related to the BOTOX or injection procedure. The AE could medically (pharmacologically/clinically) be attributed to BOTOX or injection procedure.

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.

4.6.2.7 Effectiveness Measure

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 study is planned to start after the final protocol is approved by the Drugs Controller General of India (DCGI). Per the Conditions of Additional Indication No Objection Certificate (NOC) issued by DCGI dated 19 March 2013, the study has to be completed within 1 year after the approval of the protocol by DCGI. However, the actual enrollment status will be communicated to DCGI and if needed, additional time period would be sought.

4.8 Data Management and Retention

Paper CRFs 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 CRFs, and AE reporting requirements.

The documents prepared during this study including records on the post-marketing surveillance, database, post-marketing surveillance protocol, post-marketing surveillance contract, and CRFs will be filed promptly after retrieving and retained for 10 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 (or entered into database)
- 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

- Eligible patients who were treated with BOTOX and whose safety data were collected at least on 1 post-treatment visit or phone call within the 1- to 4-month follow-up period

B. Inclusion criteria for effectiveness assessment

- Eligible 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 (ie, 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 (eg, 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 (eg, 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 frequency table by type of adverse event will be prepared. The severity, outcome, and causal relationship of AE to BOTOX, and whether or not treatment for adverse event 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.

The frequency of SAEs and non-serious AEs will be tabulated. The Medical Dictionary for Regulatory Activities (MedDRA) medical terminology will be used in data reporting at the level of 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.

5. Adminstrative Items

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 DCGI.

5.2 Reporting of Adverse Events

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, etc. will be recorded in the corresponding section in the CRF and the Allergan Non-interventional Study Adverse Event Form. A safety management plan, describing roles and responsibilities for identifying, collecting and reporting of adverse event data to 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 fax or email using the PMS Adverse Event Form (contact details can be found on page 1 of the Non-Interventional Study Adverse Event Form). Emergency phone numbers and relevant Allergan personnel contacts are also on the front page of 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 Non-interventional Study Adverse Event Form describing the event chronologically, including any treatment given (eg, 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, etc. 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 Independent Ethics Committee (IEC) of the serious adverse event as required by the IEC, local regulations, and the governing health authorities.

5.3 Human Patient 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 (eg, ICF, CRF, PMS Adverse Event Form, and communication materials) to the responsible IEC for its review. The approval of the IEC will be filed in the

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.

5.4 Reporting and Dissemination of Results

A final report will be compiled and submitted to DCGI at the end of the study. Periodic updates on the study status will be provided as per the applicable local regulations.

6. Attachments

6.1 Case Report Form

6.2 Informed Consent Form

6.3 List of Investigators (with Addresses)

6.4 Non-interventional Study Adverse Event Form

6.5 Package Insert

6.6 Glossary of Abbreviations

Term/Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
CI	confidence interval
CRF	case report form
DCGI	Drugs Controller General of India
GCP	Good Clinical Practices
ICIQ-SF	International Consultation on Incontinence Questionnaire Short Form
IEC	Independent Ethics Committee
MedDRA	Medical Dictionary for Regulatory Activities
MS	multiple sclerosis
NDO	neurogenic detrusor overactivity
NOC	No Objection Certificate
OAB	overactive bladder
PVR	post void residual
SAE	serious adverse event
SCI	spinal cord injury

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