

Drug Use Result Survey of Botox Vista[®] Injection 50 Units

How to Implement Survey and Fill out the Questionnaire

- For CFL -

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1. Purposes

This is a survey for the purposes of collecting and evaluating the information on the safety, efficacy and proper use of Botox Vista[®] Injection 50 Units (hereinafter referred to as “this product”) in adult patients aged younger than 65 years, who undergo the treatment of expression lines of lateral canthus (crow’s feet lines) during actual use. In this survey, moreover, attention will be paid to make it possible to conduct evaluation according to the following states of use to obtain the information to promote proper use, and the patient’s experience of treatment and the difference in background factors of institutions (physicians conducting injection) will be examined.

- Patients who undergo the treatment with this product for the first time (initial administration group) / Patients with an experience of the treatment with botulinum toxin type A (repeated administration group)

<Priority survey items>

Hypersensitivity reaction, Eye disorders, Neutralizing antibody formation, Administration to patients with neuromuscular disorder, Distant spread of toxin, Seizure, Interaction with drugs with muscle relaxing effects, will be established as the priority survey items.

2. Number of subjects to be surveyed

Number of subjects to be surveyed (number of patients enrolled): 1080

3. Patients to be included in the survey

Patients undergo the treatment of “Crow’s feet lines in adult patients aged less than 65 years”, an indication of this product (initial administration group and repeated administration group).

4. Survey items

1) Information of institution

Name of institution, name of department, name of physician, and the presence or absence of registration to the related academic societies such as those for plastic surgery, cosmetic surgery and cosmetic dermatology, etc.

2) Information required to identify the patient

Medical chart number (or patient identification number), patient’s initials

3) Patient’s background

Sex, date of birth or age, the presence or absence of the experience and frequency of the treatment with botulinum toxin type A, classification of inpatient or outpatient, height, body weight, reason for use, underlying disease and complication (eye disease, skin disease, renal dysfunction, hepatic dysfunction, neurological or muscular disease, respiratory disease, heart disease, and others), previous medical history, appreciable constitution, and predisposition of hypersensitivity (the patient)

4) History of treatment of facial wrinkles before the start of this survey (except for the experience of the treatment with botulinum toxin type A)

Presence or absence of the history of treatment, name of the drug/therapy used, period of treatment,

time of treatment, site of treatment, frequency of treatment, and efficacy

5) Status of administration of this product

Day of administration, site of administration, and dose (unit) at each site

6) Evaluation of efficacy

As for the degree of improvement of wrinkles after administration of this product, the following evaluation information will be collected. If administration is conducted multiple times (twice and more) during the observation period, the evaluation information will be collected for each time.

- (1) Evaluation of the degree of improvement of wrinkles by listening to the patient's evaluation
- (2) Degree of patient satisfaction
- (3) Evaluation of the severity of wrinkles by physician (before and after administration)
- (4) Overall improvement rating (evaluation by physician)

7) Concomitant drug

As for all the drugs (including the drugs prescribed at the other hospitals) used during the observation period for the purposes other than improvement of Crow's feet lines, such as the treatment of underlying diseases, complications or adverse events, the information such as name of the drug, dosage form and the reason for use will be collected.

8) Concomitant therapy

As for the therapies other than this product, used during the observation period for the purpose of improvement of wrinkles, the information such as name of the drug/therapy, daily dose, day of treatment, site of treatment and efficacy will be collected.

9) Antibody examination of botulinum toxin type A

If there is any information on antibody examination, please provide the date and result (positive or negative) of the examination.

10) Priority survey items

Hypersensitivity reaction, Eye disorders, Neutralizing antibody formation, Administration to patients with neuromuscular disorder, Distant spread of toxin, Seizure, Interaction with drugs with muscle relaxing effects, will be established as the priority survey items.

11) Presence or absence of adverse event

- (1) All the "adverse events (diseases, symptoms, abnormal laboratory test values, etc.)" which occurred after administration of this product irrespective of the relationship with this product and their relationship with this product (evaluated by 4-grade scale of "1. Definite," "2. Probable," "3. Possible" and "4. Not related")
- (2) The adverse events whose relationship with this product was evaluated as any of "1. Definite," "2. Probable" or "3. Possible" will be handled as "adverse drug reactions."

12) Drug use survey in pregnant women

The use of this product in pregnant women or possibly pregnant women is contraindicated, but if pregnancy is found after administration, the mother and her baby will be followed up to collect the information on the pregnancy progress including before and after pregnancy, delivery, miscarriage or abortion, and adverse events.

5. Observation period

6 months after administration at the start of enrollment in this survey

6. Survey period

Survey period: 2 years and 6 months from the start of marketing

Enrollment period: 2 years from the start of marketing

7. Method of survey

1) Schedule

	Start of this survey	Observation period				After 6 months
	At the initial administration *1	Second administration or later		After 6 months		
	At administration	After 1 to 8 weeks	At administration		After 1 to 8 weeks	
Enrollment of patient	• (Within 14 days from the day of initial administration *1)					
Patient's treatment history (Botulinum toxin type A preparation)	•					
Patient's background	•					
Patient's treatment history (Other than botulinum toxin type A preparation)	•					
Status of administration of this product	•		•			
Concomitant drug/therapy	←—————→					
Evaluation of severity of wrinkles at maximum frown (before administration)	• (Severity of wrinkles before administration)		• (Severity of wrinkles before administration)			
Evaluation of severity of wrinkles at maximum frown (after administration)		•*2		•*2		
Efficacy evaluation			• (First evaluation or previous evaluation)			
Adverse events	←—————→					

*1 Indicates the first administration in this survey irrespective of the history of treatment with botulinum toxin type A.

*2 Please evaluate severity of wrinkles after administration when the patient visits hospital at an appropriate time (1 to 8 weeks after each administration) and the severity of wrinkles at maximum frown can be evaluated.

2) Enrollment

The survey shall be conducted by the central enrollment method, and the physician in charge of survey shall enroll the patient administered this product and the physician who administered this product by the following procedures. Patients are enrolled **in the order administration is started** (provided, however, that the enrollment of patient is suspended for confirmation of the information of enrollment etc.).

- (1) Please provide the “name of institution,” “name of department,” “name of physician,” “presence or absence of registration to the related academic society and the name of academic society registered,” “medical chart number,” “patient’s initials,” “sex,” “date of

birth or age,” “date of initial administration in this survey” and “presence or absence of the history of treatment with botulinum toxin type A preparation and frequency of treatment” in the enrollment sheet.

As for the patient with a history of treatment, please provide the date of administration up to the past 5 times in the order of the date close to the date of initial administration in this survey. If the exact date is unknown, it is permitted to provide the year and month only.

Please follow the method below to enroll within 14 days after administration of this product (the day of initial administration shall be considered as Day 1). Medical representatives will confirm the status of enrollment as much as possible until the number of patients enrolled reaches the contracted number of patients.

<p><Method of enrollment> Pending</p>

- 2) We will send “The details of enrollment” by FAX after confirmation of the details of enrollment.
Please confirm the details of enrollment.
- 3) Filling out the questionnaire
Please fill out the questionnaire after the end of observation period with reference to “8. How to fill out the questionnaire.”
- 4) Submission of the questionnaire
Please submit the completed questionnaire to the medical representative after the end of observation period.

8. How to fill out the questionnaire

Please fill out the questionnaire with reference to the following matters:

- 1) General points to remember when filling out the questionnaire
 - (1) Please fill out the questionnaire completely.
 - (2) Please fill out the questionnaire clearly with Chinese characters in standard style using a black (or blue) ballpoint pen or pen.
 - (3) If correction is made to the questionnaire, please correct the relevant item with double line or x mark so that the original one can be made out (correction fluid is not permissible) and affix a seal (Inkan) of correction.
 - (4) In the cases of major correction and correction of important matters such as adverse event etc., please provide the reason for correction.
 - (5) Please confirm the completed questionnaire and put your signature and seal (Inkan) in the column of signature.

- (6) If the patient has not visited hospital on and after the day of administration or in the course of observation period, please follow up the presence or absence of adverse event and the reason for not visiting, etc. by telephone, etc.
- 2) Patient's background
- (1) Classification of inpatient or outpatient
Please provide the classification of inpatient or outpatient at the initial administration in this survey.
- (2) Height and body weight
Please provide the height and body weight at the initial administration in this survey.
- (3) Reason for use
Please provide the reason for use of this product.
- (4) Underlying disease and complication
Please provide information on the presence or absence of underlying disease or complication. In the case of "presence," please provide the name of disease in the applicable column. In this survey, moreover, the symptoms which have been observed since before the start of administration of this product irrespective of the relationship with the reason for use are handled as "complications."
- (5) Appreciable constitution and predisposition of hypersensitivity
Please provide information on the presence or absence of appreciable constitution and predisposition of hypersensitivity. In the case of "presence", please provide the details.
- 3) History of treatment before administration of Botox Vista Injection (experience of treatment with the drugs other than botulinum toxin type A preparation)
Please provide information on the presence or absence of the history of treatment of facial wrinkles with the drugs other than botulinum toxin type A preparation before the start of this survey. In the case of "presence," please provide the details, including name of the drug/therapy, daily dose, period of treatment, site of administration/treatment, etc. If the day of administration/treatment is unknown, please provide the frequency of administration/treatment.
- 4) Status of administration of Botox Vista Injection [first administration]
Please provide the date of the first administration, site of administration and dose (unit) at each site in this survey.
- 5) Efficacy evaluation [most recent time of injection (first administration)]
- ① Evaluation of the degree of improvement of wrinkles by listening to the patient's evaluation
As for the efficacy after the first administration in this survey, please listen to the patient's evaluation on degree of improvement of wrinkles with regard to the condition of wrinkles when the highest efficacy appeared using the improvement evaluation 9-grade scale of "+4: wrinkles were completely removed (100% better)," "+3: wrinkles became nearly less prominent (75% better)," "+2: wrinkles were removed to some extent (50% better)," "+1:

wrinkles were improved compared to before injection (25% better),” “0: no change from before injection (0% better),” “-1: wrinkles were slightly exacerbated compared to before injection (25% worse),” “-2: the condition of wrinkles was considerably exacerbated (50% worse),” “-3: the condition of wrinkles was substantially exacerbated (75% worse)” and “-4: the condition of wrinkles became worst (100% worse),” and provide the results. For reference, please also use the numerical figures when the degree of improvement/exacerbation described in the column of supplemental remarks was expressed in percentage concomitantly.

② Degree of patient satisfaction

As for the efficacy after the first administration, please listen to the degree of patient satisfaction using 7-grade scale of “+3: very satisfied,” “+2: satisfied,” “+1: rather satisfied,” “0: neither satisfied nor unsatisfied,” “-1: rather unsatisfied,” “-2: unsatisfied” and “-3: very unsatisfied” and provide the result. Please evaluate physicians’ and patients’ evaluation of the degree of improvement of wrinkles comprehensively and provide the result. If the patient has not visited hospital by the end of observation period, moreover, please conduct follow-up observation (by telephone etc.) as much as possible, and collect and provide the information on safety and efficacy.

③ Evaluation of the severity of wrinkles by physician (before and after administration)

Please evaluate the severity of wrinkles at maximum frown (when a frowny face was made by bending eyebrows with all the strength as the eyes are opened) by using 4-grade scale of “0. None,” “1. Mild,” “2. Moderate” and “3. Severe.”

As for severity of wrinkles after administration, please evaluate it when the patient visits hospital at an appropriate time 1 to 8 weeks after administration of this product and the severity of wrinkles at maximum frown can be evaluated.

④ Overall improvement rating (evaluation by physicians):

As for the efficacy of this product after the first administration, please evaluate physicians’ and patients’ evaluation of the degree of improvement of wrinkles comprehensively and determine the severity. This item is necessary. Therefore, if the patient has not visited hospital by the end of observation period, please conduct follow-up observation (by telephone etc.) as much as possible and collect and provide the information on safety and efficacy.

6) Status of administration of Botox Vista Injection [(second) and (third) injections]

Please provide information on the second administration of this product with reference to the above 4). (If the third administration is conducted within the observation period in this survey, please provide information on the third injection in the same manner.)

7) Efficacy evaluation [(second) and (third) injections]

Please provide information on the second administration of this product with reference to the

above 5). (If the third administration is conducted within the observation period in this survey, please provide information on the third injection in the same manner.)

8) Presence or absence of pregnancy

The use of this product in pregnant women or possibly pregnant women is contraindicated, but if pregnancy is found after administration, please choose “presence” and provide the expected delivery date (refer to 10. Handling of the use in pregnant women).

9) Concomitant drug

Please provide information on the presence or absence of the drugs (including the drugs prescribed by other hospitals) used during the observation period for the purposes other than improvement of Crow’s feet lines, including the treatment of underlying disease, complication or adverse event. In the case of “presence,” please provide the details of all drugs, such as the drug name, as practicably as possible.

10) Concomitant therapy

Please provide information on the presence or absence of the therapy other than this product, used during the observation period for the purpose of improvement of wrinkles. In the case of “presence,” please provide the details such as name of the drug/therapy etc.

11) Antibody examination of botulinum toxin type A

If weak improvement of wrinkles with this product is observed and an antibody examination of botulinum toxin type A is conducted for the purpose of evaluating the appropriateness of additional administration, please provide the information on the result.

12) Priority survey items: Please provide the details of following events

Hypersensitivity reaction, Eye disorders, Neutralizing antibody formation, Administration to patients with neuromuscular disorder, Distant spread of toxin, Seizure, Interaction with drugs with muscle relaxing effects

13) Presence or absence of adverse event

Please provide the details of all the adverse events (such as disease, symptom, abnormal laboratory test value, etc.) which occurred after the start of this survey, irrespective of the presence or absence of the causal relationship with this product. We will handle the adverse events whose relationship with this product is considered as “1. Definite,” “2. Probable” or “3. Possible” as “adverse drug reactions.” As for “the patient who has not visited after the day of the start of administration” and cannot be followed up by telephone etc., it is not necessary to fill out this column.

9. Handling of adverse events

- 1) As for the patients showing adverse events, we may investigate them in more details as required. Please cooperate with us on such the occasion.
- 2) If you experience adverse drug reactions of this product or serious adverse events (the events

falling under at least one item written in blue letters in the questionnaire) among adverse events, please contact our medical representative urgently.

If any serious adverse event falling under the following matters occurs, please contact our medical representative or department in charge immediately by FAX or telephone:

- (1) Death due to adverse event
- (2) Life-threatening symptoms
- (3) Symptoms requiring hospitalization or extended hospitalization for treatment
- (4) Disability (symptoms showing dysfunction interfering with daily life)
- (5) Serious symptoms conforming to (1) to (4)
- (6) Congenital disease or abnormality in the subsequent generation

An adverse event is any untoward medical occurrence in a patient administered **Botox Vista Injection** and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of **Botox Vista Injection**, whether or not considered related to **Botox Vista Injection**. Moreover, a reaction, in contrast to an event, is characterized by the fact that a causal relationship between **Botox Vista Injection** and the occurrence is suspected.

- 3) As for the patient showing adverse event, we may report the provided information to the Ministry of Health, Labour and Welfare (MHLW), our headquarters in the US or domestic or overseas affiliated companies.

If any healthcare professional with experience of similar adverse reactions inquires about the past cases of adverse reaction, moreover, we may provide information on the progress, treatment, etc. of adverse reactions in this case as reference information. For the purpose of “proper use” and “ensuring safety,” moreover, we will provide the results of aggregation and analysis of this survey to medical institutions, etc.

The information of adverse reaction, which we report to the MHLW, will be disclosed based on the Act on the Protection of Personal Information Held by Administrative Organs if requested (the Act on the Protection of Personal Information Held by Administrative Organs stipulates that “anybody can request to disclose administrative documents,” and these administrative documents include the report that we will submit to the MHLW). Moreover, the information of adverse reactions among these information will be posted on the internet as a list of cases or a list of reported adverse reactions through the Drug and Medical Device Information System of the Pharmaceuticals and Medical Devices Agency.

Among the information reported, however, those on the privacy of patients will never be disclosed. Moreover, we will never report the information on the reporting physician, such as the name of institution and reporting physician, etc. to the MHLW and medical institutions, etc. We will manage strictly the provided information based on the Act on the Protection of Personal Information.

10. Handling of the use in pregnant women

- 1) If the pregnancy of patient is found after the start of administration of this product, please contact our medical representatives.
- 2) As for the use in pregnant women, we will investigate the conditions of mother and baby around the expected delivery date, so please cooperate with us on such the occasion.

11. Disclosure of the survey result

The result of this survey may be disclosed for the purpose of “proper use” and “ensuring safety.” Among the information reported, however, we will never disclose the information on the privacy of patient.

12. Contact information of the person in charge

If you experience adverse reactions or serious adverse events of this product (events falling under at least one item written in blue letters in the questionnaire) or if you have any question about filling out the questionnaire, please contact our medical representatives.

Allergan Japan K.K.
Regulatory Affairs and Safety Department
TEL : 03-6409-5070
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13. Enrollment center

Pending