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[Attached Form 21]

Re-examination Application for Medicinal Products

Processed in 150 days

Application No.		Application Date		Issued Date	
Applicant	Business License (Importer Confirmation) Number	[redacted]			
	Name of Manufacturing (Business) Site	Allergan Korea Ltd.			
	Address of Manufacturing (Business) Site	14F, GT Tower East, Seocho-daero 411, Seocho-gu, Seoul, Korea (06615)			
	Name	[redacted]	[redacted]	[redacted]	
Manufacturer	Name of Manufacturing Site	Allergan Pharmaceuticals Ireland	Manufacturing Country	Ireland	
	Address	Allergan Pharmaceuticals Ireland, Castlebar Road, Westport, County Mayo, Ireland			
Product Name for Re-examination		Botox Inj. 50 units (Clostridium Botulinum Toxin Type A)	Re-examination Period	Feb 04, 2014 ~ Feb 03, 2018 (4 years)	
Approval Number		No.10	Approval Date	Mar 03,2009	
Surveillance	Period and Number of Subjects	Surveillance period: Feb 04, 2014 ~ Feb 03, 2018 (4 years) Number of subjects whose CRFs were retrieved: 695 Number of subjects included in the analysis set: 667 Number of subjects included in the effectiveness analysis set: 376			
	Summary and Interpretation of Results	Refer to Post Marketing Surveillance Re-examination Report			
Production Results (Release Results)		Refer to "Ⅶ Shipping Record" in Post Marketing Surveillance Re-examination Report			

In compliance with Article 32 of [Pharmaceutical Affairs Act] and Article 23, paragraph 1 of [Regulations on Safety of Pharmaceuticals, etc.], we would like to apply for a re-examination of the pharmaceutical drug as above.

MMM DD, 2018

[redacted]

To Minister of Food and Drug Safety

Attachments	Fee
1. Periodic report in compliance with Clause A, Subparagraph 8 of [Post-marketing safety management standards for Medicinal Products, etc.], included in the Appendix Table 3 of 4, Article 24 of [Regulations on Safety of Pharmaceuticals, etc.] 2. A comprehensive analysis/evaluation on the result of periodic report above.	Amount notified by the Minister of Food and Drug Safety

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Botox®Inj. 50 units
Post Marketing Surveillance
Re-examination Report

(Botox® Inj. 50 units,

Clostridium Botulinum Toxin Type A Neurotoxin)

Re-examination Period: Feb 04, 2014 ~ Feb 03, 2018

Allergan Korea Ltd.

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[Annexes]

1. Post Marketing Surveillance Study Protocol (Version 1.0)

2. Case Report Form (Version 1.0)

3. A Copy of Product License (27 Feb 2018)

4. Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report

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5. Subjects excluded from the safety analysis set for Demographic characteristics

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Ⅰ. PMS Overview

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1. PMS Overview

1.1 Re-examination period

Feb 04, 2014 ~ Feb 03, 2018

1.2 Number of subjects

During the re-examination period, case report forms (CRFs) were collected for a total of 695 subjects. Among the subjects whose CRFs were retrieved, a total of 667 subjects were included in the safety analysis set after excluding 10 subjects who were 'Foreigners (not Korean)', 1 subject who was 'Duplicate', 5 subjects who 'didn't receive BOTOX for this study', 11 subjects for 'Follow-up failure', and 1 subject who 'Violated the usage/dosage'. Of the 667 subjects, 376 subjects were included in the effectiveness analysis set after excluding 277 subjects with 'Missing information of overall assessment of change in crow's feet lines by the investigator', 1 subject who 'receive a subsequent BOTOX injection before overall assessment of change in crow's feet lines by the investigator', and 13 subjects who were 'collected effectiveness evaluations beyond 3 months after the index BOTOX injection'.

No. of subjects whose CRFs were retrieved	695
No. of subjects included in the safety analysis set	667
No. of subjects included in the effectiveness analysis set	376

Number of sites	From 04 Feb 2014 to 03 Feb 2018, CRFs of 695 subjects were retrieved by 26 investigators at 26 institutions.
Study method	All subjects who received Botox® Inj. 50 units were to be included in this study in a continuous manner from the date of contract until the planned number of subjects was enrolled.
Case report form	Annex 2
Study focus +	There was no specific focus in this study since no specific issues had been identified in clinical study results during the development. During this re-examination period, very rarely occurring adverse events (AEs) and unexpected AEs of which causal relationship to the study drug had not been established were to be monitored and investigated with particular interest.

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Ⅱ. Overview of PMS Results

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2. Overview of PMS Results

2.1 Overview and purpose of PMS

This surveillance study was conducted in adult patients aged between 18 to 75 with moderate to severe lateral canthal lines (crow's feet lines) who were treated with the Botox® Inj. 50 units (hereinafter 'the study drug') in order to investigate the onset and incidence status of unexpected adverse events and serious adverse events, the frequency and change of adverse events, and the factors that may affect the safety and effectiveness of the study drug in the post marketing setting.

The data on indications for 'moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity' was collected from 31 Mar 2009 until 01 Jul 2012, which included the remaining period of re-examination. As the re-examination report was completed, no data was collected in this surveillance..

This study examined demographic chracteristics, past treatment history, medical history, concomitant medications, special populations, and information related to the study drug injection of the study subjects (full analysis set, safety analysis set, and subjects excluded from the safety analysis set). This study was planned to investigate all types of adverse events occurring during the study period, including unexpected adverse events as well as very rarely occurring adverse events without causal relationship established to the study drug. The purpose of this study was to carefully monitor and investigate the incidence of adverse events.

2.2 Demographic characteristics

2.2.1 Full analysis set

The mean age of 695 subjects in the full analysis set was 41.23±12.98 years, ranging from 20 to 75 years. For age distribution, the majority of subjects (29.06%; 202/695 subjects) was '30 ~ 39 years', followed by (21.73%; 151/695 subjects) '20 ~ 29 years', and (21.29%; 148/695 subjects) '40 ~ 49 years' (Table 1).

In the full analysis set, when the subjects of '65 years or/and over' were classified as the elderly group, the results was 5.61% (39/695 subjects) (Table 1).

In the full analysis set, 'Female' accounted for 87.05% (605/695 subjects) and 'Male' accounted for 12.95% (90/695 subjects) (Table 1).

The mean height of the subjects in the full analysis set was 162.95 ± 6.52 cm and mean weight was 56.20±9.16 kg (Table 1).

There were no pregnant women in the full analysis set. No subjects became pregnant after receiving the study drug (Table 1).

Treatment indications for the subjects in the full analysis set included 'moderate to severe lateral canthal lines (crow's feet lines) associated with orbicularis oculi activity' accounting for 68.92% (479/695 subjects) and 'moderate to severe crow's feet lines and glabellar lines, when treated simultaneously' accounting for 31.08% (216/695 subjects) (Table 1).

Table 1. Demographic baseline data (Full analysis set)

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		Total n (%)
Age	mean±std (years)	41.23 ± 12.98
	median	39.00
	min ~ max	20.00 ~ 75.00
	< 20 years	0 (0.00)
	20 years ~ 29 years	151 (21.73)
	30 years ~ 39 years	202 (29.06)
	40 years ~ 49 years	148 (21.29)
	50 years ~ 59 years	122 (17.55)
	≥ 60 years	72 (10.36)
	Total	695 (100.00)
Elderly	below 65 years	656 (94.39)
	65 years or/and over	39 (5.61)
	Total	695 (100.00)
Sex	Male	90 (12.95)
	Female	605 (87.05)
	Total	695 (100.00)
Height	Unknown	190
	Known	505
	mean±std (cm)	162.95 ± 6.52
	Median	162.00
	min ~ max	147.00 ~ 184.00
	Total	695
Weight	Unknown	210
	Known	485
	mean±std (kg)	56.20 ± 9.16
	median	54.00
	min ~ max	37.00 ~ 93.00
	Total	695
Currently pregnant*	Yes	0 (0.00)
	No	605 (100.00)
	Total	605 (100.00)
Pregnancy since the index BOTOX treatment*	Yes	0 (0.00)
	No	591 (97.69)
	Missing	14 (2.31)
	Total	605 (100.00)
Treatment indication	moderate to severe lateral canthal lines associated with orbicularis oculi activity	479 (68.92)
	moderate to severe crow's feet lines and glabellar lines, when treated simultaneously	216 (31.08)
	Total	695 (100.00)

The denominator is number of total subjects

* For female

2.2.2 Safety analysis set

The mean age of 667 subjects in the safety analysis set was 40.90±12.95 years, ranging from 20 to 75 years. For age distribution, the majority of subjects (29.24%; 195/667 subjects) was '30 ~ 39 years', followed by (22.64%; 151/667 subjects) '20 ~ 29 years', and (21.29%; 142/667 subjects) '40 ~ 49 years' (Table 2).

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In the safety analysis set, when the subjects of '65 years or/and over' were classified as the elderly group, the results was 5.40% (36/667 subjects) (Table 2).

In the safety analysis set, 'Female' accounted for 87.26% (582/667 subjects) and 'Male' accounted for 12.74% (85/667 subjects) (Table 2).

The mean height of the subjects in the safety analysis set was 162.93±6.45 cm and mean weight was 56.09±9.13 kg (Table 2).

There were no pregnant women in the safety analysis set. No subjects became pregnant after receiving the study drug (Table 2).

Treatment indications for the subjects in the safety analysis set included 'moderate to severe lateral canthal lines (crow's feet lines) associated with orbicularis oculi activity' accounting for 69.87% (466/667 subjects) and 'moderate to severe crow's feet lines and glabellar lines when treated simultaneously' accounting for 30.13% (201/667 subjects) (Table 2).

Table 2. Demographic baseline data (Safety analysis set)

		Total n (%)
Age	mean±std (years)	40.90 ± 12.95
	median	39.00
	min ~ max	20.00 ~ 75.00
	< 20 years	0 (0.00)
	20 years ~ 29 years	151 (22.64)
	30 years ~ 39 years	195 (29.24)
	40 years ~ 49 years	142 (21.29)
	50 years ~ 59 years	110 (16.49)
	≥ 60 years	69 (10.34)
	Total	667 (100.00)
Elderly	below 65 years	631 (94.60)
	65 years or/and over	36 (5.40)
	Total	667 (100.00)
Sex	Male	85 (12.74)
	Female	582 (87.26)
	Total	667 (100.00)
Height	Unknown	186
	Known	481
	mean±std (cm)	162.93 ± 6.45
	median	162.00
	min ~ max	147.00 ~ 184.00
	Total	667
Weight	Unknown	206
	Known	461
	mean±std (kg)	56.09 ± 9.13
	median	54.00
	min ~ max	37.00 ~ 93.00
	Total	667
Currently pregnant*	Yes	0 (0.00)
	No	582 (100.00)

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		Total n (%)
	Total	582 (100.00)
Pregnancy since the index BOTOX treatment*	Yes	0 (0.00)
	No	582 (100.00)
	Total	582 (100.00)
Treatment indication	moderate to severe lateral canthal lines associated with orbicularis oculi activity	466 (69.87)
	moderate to severe crow's feet lines and glabellar lines, when treated simultaneously	201 (30.13)
	Total	667 (100.00)

The denominator is number of total subjects

* For female

2.2.3 Subjects excluded from the safety analysis set

The mean age of 28 subjects excluded from the safety analysis set was 49.07±11.21 years, ranging from 30 to 73 years. For age distribution, the majority of subjects (42.86%, 12/28 subjects) was '50 ~ 59 years', followed by (25.00%, 7/28 subjects) '30 ~ 39 years', and (21.43%, 6/28 subjects) '40 ~ 49 years'.

In the subjects excluded from the safety analysis set, when the subjects of '65 years or/and over' were classified as the elderly group, the results was 10.71% (3/28 subjects).

In the subjects excluded from the safety analysis set, 'Female' accounted for 82.14% (23/28 subjects) and 'Male' accounted for 17.86% (5/28 subjects).

There were no pregnant women among the subjects excluded from the safety analysis set. None of the subjects became pregnant after receiving the study drug.

Please refer to [Annex 5] further information.

2.3 Past treatment history

2.3.1 Full analysis set

In the full analysis set, 9.64% (67/695 subjects) had a history of facial aesthetic procedures (excluding the study drug) within the past 6 months (Table 3).

In the full analysis set, 9.35% (65/695 subjects) had a history of other nontoxin or nonperiocular facial aesthetic or dermatologic treatment at baseline visit (Table 3).

In the full analysis set, 13.96% (97/695 subjects) had a history of study drug or other botulinum toxin use within the past 6 months (Table 3).

Table 3. Past treatment history (Full analysis set)

		Total

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		n (%)
History of facial aesthetic procedure (excluding BOTOX) in the past 6 months	Yes	67 (9.64)
	No	628 (90.36)
	Total	695 (100.00)
Other nontoxin or nonperiocular facial aesthetic or dermatologic treatment at current visit	Yes	65 (9.35)
	None	630 (90.65)
	Total	695 (100.00)
Past BOTOX or other botulinum toxin in the past 6 months	Yes	97 (13.96)
	None	598 (86.04)
	Total	695 (100.00)

The denominator is number of total subjects

2.3.2 Safety analysis set

In the safety analysis set, 9.45% (63/667 subjects) had a history of facial aesthetic procedures (excluding the study drug) within the past 6 months (Table 4).

In the safety analysis set, 9.75% (65/667 subjects) had a history of other nontoxin or nonperiocular facial aesthetic or dermatologic treatment at baseline visit (Table 4).

In the safety analysis set, 14.09% (94/667 subjects) had a history of study drug or other botulinum toxin use within the past 6 months (Table 4).

Table 4. Past treatment history (Safety analysis set)

		Total n (%)
History of facial aesthetic procedure (excluding BOTOX) in the past 6 months	Yes	63 (9.45)
	No	604 (90.55)
	Total	667 (100.00)
Other nontoxin or nonperiocular facial aesthetic or dermatologic treatment at current visit	Yes	65 (9.75)
	None	602 (90.25)
	Total	667 (100.00)
Past BOTOX or other botulinum toxin in the past 6 months	Yes	94 (14.09)
	None	573 (85.91)
	Total	667 (100.00)

The denominator is number of total subjects

2.3.3 Subjects excluded from the safety analysis set

In the subjects excluded from the safety analysis set, 14.29% (4/28 subjects) had a history of facial aesthetic procedures (excluding the study drug) within the past 6 months.

In the subjects excluded from the safety analysis set, no subject had a history of other nontoxin or nonperiocular facial aesthetic or dermatologic treatment at baseline visit.

In the subjects excluded from the safety analysis set, 10.71% (3/28 subjects) had a history of study drug or other botulinum toxin use within the past 6 months.

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Please refer to [Annex 5] further information.

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2.4 Medical history

2.4.1 Full analysis set

In the full analysis set, 10.65% (74/695 subjects) had other medical history including surgeries and complications of underlying diseases (Table 5).

Analyzing the detailed medical history of the subjects in the full analysis set, allowing overlapped counting, 24.32% (18/74 subjects) had 'Diseases of the eye and adnexa', 20.27% (15/74 subjects) had 'Endocrine, nutritional and metabolic diseases' and 'Factors influencing health status and contact with health services' respectively, and 14.86% (11/74 subjects) had 'Diseases of the musculoskeletal system and connective tissue' (Table 5).

In the full analysis set, 3.12% (21/695 subjects) had history of allergies (Table 5).

Table 5. Medical history (Full analysis set)

		Total n (%)
Medical History, Including Surgeries and Complications of Underlying Diseases	Yes	74 (10.65)
	None	621 (89.35)
	Total	695 (100.00)
	Details for Medical History by dictionary (Overlapped*)	
	Diseases of the eye and adnexa	18 (24.32)
	Endocrine, nutritional and metabolic diseases	15 (20.27)
	Factors influencing health status and contact with health services	15 (20.27)
	Diseases of the musculoskeletal system and connective tissue	11 (14.86)
	Diseases of the circulatory system	10 (13.51)
	Diseases of the skin and subcutaneous tissue	9 (12.16)
	Diseases of the respiratory system	8 (10.81)
	Neoplasms	8 (10.81)
	Diseases of the digestive system	7 (9.46)
	Certain infectious and parasitic diseases	5 (6.76)
	Diseases of the genitourinary system	4 (5.41)
	Diseases of the nervous system	2 (2.70)
	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1 (1.35)
	Injury, poisoning and certain other consequences of external causes	1 (1.35)
	Mental and behavioural disorders	1 (1.35)
	Symptoms, signs and abnormal clinical and laboratory findings, NEC	1 (1.35)
History of Allergies	Yes	21 (3.12)
	None	674 (100.00)
	Total	695 (103.12)

The denominator for 'Yes/None' is number of total subjects
The denominator for details is number of subjects in 'Yes'
Dictionary: KCD
* The same subject may appear in different categories

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2.4.2 Safety analysis set

In the safety analysis set, 10.49% (70/667 subjects) had other medical history including surgeries and complications of underlying diseases (Table 6).

Analyzing the detailed medical history of the subjects in the safety analysis set, allowing overlapped counting, 25.71% (18/70 subjects) had 'Diseases of the eye and adnexa', 20.00% (14/70 subjects) had 'Factors influencing health status and contact with health services', and 18.57% (13/70 subjects) had 'Endocrine, nutritional and metabolic diseases' (Table 6).

In the safety analysis set, 3.00% (20/667 subjects) had history of allergies (Table 6).

Table 6. Medical history (Safety analysis set)

		Total n (%)
Medical History, Including Surgeries and Complications of Underlying Diseases	Yes	70 (10.49)
	None	597 (89.51)
	Total	667 (100.00)
	Details for Medical History by dictionary (Overlapped*)	
	Diseases of the eye and adnexa	18 (25.71)
	Endocrine, nutritional and metabolic diseases	13 (18.57)
	Factors influencing health status and contact with health services	14 (20.00)
	Diseases of the musculoskeletal system and connective tissue	11 (15.71)
	Diseases of the circulatory system	7 (10.00)
	Diseases of the skin and subcutaneous tissue	8 (11.43)
	Diseases of the respiratory system	8 (11.43)
	Neoplasms	7 (10.00)
	Diseases of the digestive system	7 (10.00)
	Certain infectious and parasitic diseases	5 (7.14)
	Diseases of the genitourinary system	3 (4.29)
	Diseases of the nervous system	2 (2.86)
	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	1 (1.43)
	Injury, poisoning and certain other consequences of external causes	1 (1.43)
	Mental and behavioural disorders	1 (1.43)
History of Allergies	Yes	20 (3.00)
	None	647 (97.00)
	Total	667 (100.00)

The denominator for 'Yes/None' is number of total subjects
The denominator for details is number of subjects in 'Yes'
Dictionary: KCD
* The same subject may appear in different categories

2.4.3 Subjects excluded from the safety analysis set

In the subjects excluded from the safety analysis set, 14.29% (4/28 subject) had other medical history including surgeries and complications of underlying diseases.

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In the subjects excluded from the safety analysis set, 3.57% (1/28 subjects) had history of allergies.

Please refer to [Annex 5] further information.

2.5 Concomitant medications

2.5.1 Full analysis set

In the full analysis set, 8.63% (60/695 subjects) had received concomitant medications and/or other botulinum toxins excluding the study drug (Table 7).



Analyzing the types of concomitant medications in the full analysis set, allowing overlapped counting, 26.67% (16/60 subjects) had 'Cardiovascular & Hematopoietic System', 25.00% (15/60 subjects) had 'Gastrointestinal & Hepatobiliary System' and 'Musculo-Skeletal System' respectively, and 16.67% (10/60 subjects) had 'Anti-infectives (systemic)' and 'Central Nervous System' respectively (Table 7).

Table 7. Concomitant medications and other botulinum toxins except the study drug (Full analysis set)

	Total n (%)
Yes	60 (8.63)
None	635 (91.37)
Total	695 (100.00)
Details for Concomitant Medication by dictionary (Overlapped*)	
Cardiovascular & Hematopoietic System	16 (26.67)
Miscellaneous	3 (5.00)
Anticoagulants, Antiplatelets & Fibrinolytics (Thrombolytics)	3 (5.00)
Diuretics	3 (5.00)
Dyslipidaemic Agents	3 (5.00)
Other Antihypertensives	3 (5.00)
Angiotensin Ⅱ Antagonists	1 (1.67)
Beta-Blockers	1 (1.67)
Calcium Antagonists	1 (1.67)
Phlebitis & Varicose Preparations	1 (1.67)
Gastrointestinal & Hepatobiliary System	15 (25.00)
Antacids, Antireflux Agents & Antiulcerants	9 (15.00)
GIT Regulators, Antiflatulents & Anti-inflammatories	3 (5.00)
Cholagogues, Cholelitholytics & Hepatic Protectors	2 (3.33)
Digestives	2 (3.33)
Laxatives, Purgatives	1 (1.67)
Musculo-Skeletal System	15 (25.00)
Muscle Relaxants	12 (20.00)
Other Drugs Acting on the Musculo-Skeletal System	2 (3.33)
Disease-Modifying Anti-Rheumatic Drugs (DMARDs)	1 (1.67)

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	Total n (%)
Anti-infectives (systemic)	10 (16.67)
Cephalosporins	3 (5.00)
Tetracyclines	3 (5.00)
Anti-TB Agents	1 (1.67)
Antibacterial Combinations	1 (1.67)
Antifungals	1 (1.67)
Antivirals	1 (1.67)
Macrolides	1 (1.67)
Central Nervous System	10 (16.67)
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	7 (11.67)
Analgesics (Non-Opioid) & Antipyretics	2 (3.33)
Drugs For Neuropathic Pain	2 (3.33)
Hypnotics & Sedatives	1 (1.67)
Endocrine & Metabolic System	9 (15.00)
Thyroid Hormones	5 (8.33)
Antidiabetic Agents	2 (3.33)
Other Agents Affecting Metabolism	2 (3.33)
Anti-obesity Agents	1 (1.67)
Antithyroid Agents	1 (1.67)
Allergy & Immune System	7 (11.67)
Antihistamines & Antiallergics	7 (11.67)
Vitamins & Minerals	6 (10.00)
Calcium / with Vitamins	5 (8.33)
Vitamins & Minerals (Pre & Post Natal) / Antianemics	2 (3.33)
Vitamins A, D & E	1 (1.67)
Hormones	5 (8.33)
Corticosteroid Hormones	4 (6.67)
Oestrogens & Progesterones & Related Synthetic Drugs	1 (1.67)
Dermatologicals	3 (5.00)
Acne Treatment Preparations	3 (5.00)
Eye	3 (5.00)
Eye Corticosteroids	2 (3.33)
Ophthalmic Lubricants	2 (3.33)
Oncology	3 (5.00)
Hormonal Chemotherapy	2 (3.33)
Cytotoxic Chemotherapy	1 (1.67)
Respiratory System	2 (3.33)
Antiasthmatic & COPD Preparations	1 (1.67)
Cough & Cold Preparations	1 (1.67)
Genito-Urinary System	1 (1.67)
Drugs for Erectile Dysfunction and Ejaculatory Disorders	1 (1.67)
Miscellaneous	2 (3.33)
Miscellaneous	2 (3.33)

The denominator for 'Yes/None' is number of total subjects
The denominator for details is number of subjects in 'Yes'
Dictionary: KIMS
* The same subject may appear in different categories

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2.5.2 Safety analysis set

In the safety analysis set, 8.40% (56/667 subjects) had received concomitant medications and/or other botulinum toxins excluding the study drug (Table 8).



Analyzing the types of concomitant medications in the safety analysis set, allowing overlapped counting, 26.79% (15/56 subjects) had 'Gastrointestinal & Hepatobiliary System' and 'Musculo-Skeletal System' respectively, 21.43% (12/56 subjects) had 'Cardiovascular & Hematopoietic System', and 17.86% (10/56 subjects) had 'Anti-infectives (systemic)' and 'Central Nervous System' respectively (Table 8).

Table 8. Concomitant medications and other botulinum toxins except the study drug (Safety analysis set)

	Total n (%)
Yes	56 (8.40)
None	611 (91.60)
Total	667 (100.00)
Details for Concomitant Medication by dictionary (Overlapped*)	
Cardiovascular & Hematopoietic System	12 (21.43)
Anticoagulants, Antiplatelets & Fibrinolytics (Thrombolytics)	3 (5.36)
Diuretics	3 (5.36)
Dyslipidaemic Agents	3 (5.36)
Other Antihypertensives	3 (5.36)
Angiotensin Ⅱ Antagonists	1 (1.79)
Beta-Blockers	1 (1.79)
Phlebitis & Varicose Preparations	1 (1.79)
Gastrointestinal & Hepatobiliary System	15 (26.79)
Antacids, Antireflux Agents & Antiulcerants	9 (16.07)
GIT Regulators, Antiflatulents & Anti-inflammatories	3 (5.36)
Cholagogues, Cholelitholytics & Hepatic Protectors	2 (3.57)
Digestives	2 (3.57)
Laxatives, Purgatives	1 (1.79)
Musculo-Skeletal System	15 (26.79)
Muscle Relaxants	12 (21.43)
Other Drugs Acting on the Musculo-Skeletal System	2 (3.57)
Disease-Modifying Anti-Rheumatic Drugs (DMARDs)	1 (1.79)
Anti-infectives (systemic)	10 (17.86)
Cephalosporins	3 (5.36)
Tetracyclines	3 (5.36)
Anti-TB Agents	1 (1.79)
Antibacterial Combinations	1 (1.79)
Antifungals	1 (1.79)
Antivirals	1 (1.79)
Macrolides	1 (1.79)
Central Nervous System	10 (17.86)
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	7 (12.50)

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	Total n (%)
Analgesics (Non-Opioid) & Antipyretics	2 (3.57)
Drugs For Neuropathic Pain	2 (3.57)
Hypnotics & Sedatives	1 (1.79)
Endocrine & Metabolic System	9 (16.07)
Thyroid Hormones	5 (8.93)
Antidiabetic Agents	2 (3.57)
Other Agents Affecting Metabolism	2 (3.57)
Anti-obesity Agents	1 (1.79)
Antithyroid Agents	1 (1.79)
Allergy & Immune System	7 (12.50)
Antihistamines & Antiallergics	7 (12.50)
Vitamins & Minerals	6 (10.71)
Calcium / with Vitamins	5 (8.93)
Vitamins & Minerals (Pre & Post Natal) / Antianemics	2 (3.57)
Vitamins A, D & E	1 (1.79)
Hormones	5 (8.93)
Corticosteroid Hormones	4 (7.14)
Oestrogens & Progesterones & Related Synthetic Drugs	1 (1.79)
Dermatologicals	3 (5.36)
Acne Treatment Preparations	3 (5.36)
Eye	3 (5.36)
Eye Corticosteroids	2 (3.57)
Ophthalmic Lubricants	2 (3.57)
Oncology	3 (5.36)
Hormonal Chemotherapy	2 (3.57)
Cytotoxic Chemotherapy	1 (1.79)
Respiratory System	2 (3.57)
Antiasthmatic & COPD Preparations	1 (1.79)
Cough & Cold Preparations	1 (1.79)
Genito-Urinary System	1 (1.79)
Drugs for Erectile Dysfunction and Ejaculatory Disorders	1 (1.79)
Miscellaneous	2 (3.57)
Miscellaneous	2 (3.57)

The denominator for 'Yes/None' is number of total subjects
The denominator for details is number of subjects in 'Yes'
Dictionary: KIMS
* The same subject may appear in different categories

2.5.3 Subjects excluded from the safety analysis set

In the subjects excluded from the safety analysis set, 14.29% (4/28 subjects) had received concomitant medications and/or other botulinum toxins excluding the study drug.

Please refer to [Annex 5] further information.

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2.6 Special population

2.6.1 Full analysis set

Among the full analysis set, the analysis result of elderly subjects (≤ 65 years) is presented in Table 1.

In the full analysis set, 0.14% (1/695 subjects) had renal impairment of 'chronic renal failure' (Table 9).

In the full analysis set, 0.14% (1/695 subjects) had hepatic impairment of 'hepatitis C' (Table 9).

Table 9. Special population (Full analysis set)

		Total n (%)
Renal impairment	Yes	1 (0.14)
	No	694 (99.86)
	Total	695 (100.00)
Hepatic impairment	Yes	1 (0.14)
	No	694 (99.86)
	Total	695 (100.00)

The denominator is number of total subjects

2.6.2 Safety analysis set

Among the safety analysis set, the analysis result of elderly subjects (≤ 65 years) is presented in Table 2.

In the safety analysis set, 0.15% (1/667 subjects) had renal impairment of 'chronic renal failure' (Table 10).

In the safety analysis set, 0.15% (1/667 subjects) had hepatic impairment of 'Hepatitis C' (Table 10).

Table 10. Special population (Safety analysis set)

		Total n (%)
Renal impairment	Yes	1 (0.15)
	No	666 (99.85)
	Total	667 (100.00)
Hepatic impairment	Yes	1 (0.15)
	No	666 (99.85)
	Total	667 (100.00)

The denominator is number of total subjects

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2.6.3 Subjects excluded from the safety analysis set

Among the excluded from the safety analysis set, 10.71% (3/28 subjects) was accounted for elderly subjects (≤ 65 years).

There were no subjects with renal or hepatic impairment in the subjects excluded from the safety analysis set.

Please refer to [Annex 5] further information.

2.7 Information related to the study drug injection

2.7.1 Full analysis set

Analyzing the number of injection sites and injection units for each indications in the full analysis set, 478 subjects had treatment indication for lateral canthal lines. Among these, 477 subjects were administered the study drug in '6 sites' with '24 units' and 1 subject was administered the study drug in '6 sites' with 'other' units. 211 subjects had indication for lateral canthal lines and glabellar lines treatment simultaneously. Among these, 206 subjects were administered the study drug in '6 + 5 sites' with '24 + 20 units', 4 subjects were administered the study drug in '6 + 5 sites' with 'other' units, and 1 subject was administered the study drug in 'other' sites with 'other' units. 6 subjects with other indications were administered the study drug in 'other' sites with 'other' units (Table 11).

In the full analysis set, 0.29% (2/695 subjects) received the additional dose of the study drug after the administration of the study drug (Table 11).

Table 11. Information related to the study drug injection (Full analysis set)

		Total n (%)
Number of injection sites	6 sites(Crow's feet lines)	478 (68.78)
	6+5 sites(Glabellar lines if treated simultaneously with crow's feet lines)	210 (30.22)
	Other	7 (1.01)
	Total	695 (100.00)
Total units injected	24 units(Crow's feet lines)	477 (68.63)
	24+20 units(Glabellar lines if treated simultaneously with crow's feet lines)	206 (29.64)
	Other	12 (1.73)
	Total	695 (100.00)
Received additional BOTOX treatment since the index BOTOX treatment	Yes	2 (0.29)
	No	677 (97.41)
	Missing	16 (2.30)
	Total	695 (100.00)

The denominator is number of total subjects

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2.7.2 Safety analysis set

Analyzing the number of injection sites and injection units for each indications in the safety analysis set, all 466 subjects with treatment indication for lateral canthal lines were administered the study drug in '6 sites' with '24 units'. Among the subjects with indication for lateral canthal lines and glabellar lines treatment simultaneously, all 201 subjects were administered the study drug in '6 + 5 sites' with '24 + 20 units' (Table 12).

In the safety analysis set, 0.30% (2/667 subjects) received the additional dose of the study drug after the administration of the study drug (Table 12).

Table 12. Information related to the study drug injection (Safety analysis set)

		Total n (%)
Number of injection sites	6 sites(Crow's feet lines)	466 (69.87)
	6+5 sites(Glabellar lines if treated simultaneously with crow's feet lines)	201 (30.13)
	Total	667 (100.00)
Total units injected	24 units(Crow's feet lines)	466 (69.87)
	24+20 units(Glabellar lines if treated simultaneously with crow's feet lines)	201 (30.13)
	Total	667 (100.00)
Received additional BOTOX treatment since the index BOTOX treatment	Yes	2 (0.30)
	No	665 (99.70)
	Total	667 (100.00)

The denominator is number of total subjects

2.7.3 Subjects excluded from the safety analysis set

Analyzing the number of injection sites and injection units for individual indications in the subjects excluded from the safety analysis set, 12 subjects had treatment indication for lateral canthal lines. Among these, 11 subjects were administered the study drug in '6 sites' with '24 units' and 1 subject was administered the study drug in '6 sites' with 'other' units. 10 subjects had indication for lateral canthal lines and glabellar lines treatment simultaneously. Among these, 5 subjects were administered the study drug in '6 + 5 sites' with '24 + 20 units', 4 subjects were administered the study drug in '6 + 5 sites' with 'other' units, and 1 subject was administered the study drug in 'other' sites with 'other' units. 6 subjects with other indications were administered the study drug in 'other' sites with 'other' units.

In the subjects excluded from safety analysis set, there were no subjects who received the additional dose of the study drug after the administration of the study drug.

Please refer to [Annex 5] further information.

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Ⅲ. Results of PMS

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3. Results of PMS

3.1 Incidence of adverse events

Source: Post marketing surveillance (PMS)
Events to be reported: All adverse events (AEs) occurring in subjects during the entire surveillance period were to be included in the report, regardless of their causal relationship to the study drug.

It was specified that any AEs, which occurred during the PMS period, should be reported by the physician (investigator) to Allergan Korea Ltd. irrespective of their causal relationship with the study drug, and of these, any serious adverse events (SAEs) should be reported to Korea Institute of Drug Safety & Risk Management in accordance with established procedures.

In this report, classification of AEs was presented in accordance with the WHO-ART 092 classification criteria.

During the surveillance period, 14 AEs occurred in 11 out of 667 subjects in the safety analysis set, showing an incidence proportion of 1.65% (Table 13).

Table 13. Incidence of AEs (Safety analysis set)

Incidence* n (%)	95% CI† (Lower , Upper)	No. of AE	Total n (%)
11 (1.65)	(0.68 , 2.62)	14	667 (100.00)

* The percentage of 'Incidence of AE' = (No. subjects of AE/No. subjects of safety analysis sets)*100%
† 95% Confidence Interval for adverse event incidence is calculated using the normal approximation method.

Safety analysis was planned to be conducted on the full analysis set, the safety analysis set, and the subjects excluded from the safety analysis set. However, tendency of AE incidence by factors and detailed classification of AEs were planned to be analyzed in the safety analysis set only.

Among the 695 subjects whose CRFs were retrieved during the surveillance period, a total of 678 subjects were included in the full analysis set after excluding 1 subject who was 'Duplicate', 5 subjects who 'didn't receive BOTOX for this study', and 11 subjects of 'Follow-up failure'.

Subjects who were 'Foreigners (not Korean)' and subjects who 'Violated usage/dosage' were included as exclusion criteria for the safely analysis set according to 'Guideline for re-examination criteria for new drugs, etc.' by MFDS. Therefore, a total of 28 subjects including 10 subjects who were 'Foreigners', 1 subject who was 'Duplicate', 5 subjects who 'didn't receive BOTOX for this study', 11 subjects of 'Follow-up failure', and 1 subject who 'Violate usage/dosage' were excluded from the safety analysis.

With the exception of 28 subjects in Full analysis set, 667 subjects were analyzed for safety analysis set.

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3.1.1 Adverse events·adverse drug reactions

A. Full analysis set

During the surveillance period, 14 AEs were reported in 11 out of 678 subjects (1.62%) in the full analysis set (Table 14).

When analyzing AEs by system organ class (SOC), most common AEs included 'Application site disorders' and 'Central & peripheral nervous system disorders' in 0.44% each (3/678 subjects), followed by 'Body as a whole - general disorders', 'Platelet, bleeding & clotting disorders', and 'Skin and appendages disorders' in 0.29% each (2/678 subjects), and 'Gastro-intestinal system disorders' and 'Urinary system disorders' in 0.15% each (1/678 subjects) (Table 14).

In the detailed analysis of reported AEs, 'EYELID PTOSIS', 'INJECTION SITE PAIN' and 'BRUISE' occurred in 0.29 % each (2/678 subjects, 2 cases each), 'MEDICINE INEFFECTIVE', 'TUBERCULOSIS', 'BURNING SENSATION', 'INJECTION SITE SWELLING', 'NAIL DISORDER', 'RASH ERYTHEMATOUS', 'CONSTIPATION', and 'RENAL FAILURE ACUTE' occurred in 0.15% each (1/678 subjects, 1 case each) (Table 14).

Among these, 2 cases from 2 subjects (0.29%) were adverse drug reactions (ADRs) for which causal relationship to the study drug could not be excluded (Table 14).

The reported ADRs included 'INJECTION SITE PAIN' under "Application site disorders" in 0.29% (2/678 subjects, 2 cases) (Table 14).

Table 14. Incidence of AEs·ADRs (Full analysis set)

	AE			ADR*		
	Incidence† n (%)	95% CI§ (Lower , Upper)	No. of AE	Incidence‡ n (%)	95% CI§ (Lower , Upper)	No. of AE
Application site disorders	3 (0.44)	(0.00 , 0.94)	3	2 (0.29)	(0.00 , 0.70)	2
INJECTION SITE PAIN	2 (0.29)	(0.00 , 0.70)	2	2 (0.29)	(0.00 , 0.70)	2
INJECTION SITE SWELLING	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Central & peripheral nervous system disorders	3 (0.44)	(0.00 , 0.94)	3	0 (0.00)	(0.00 , 0.00)	0
EYELID PTOSIS	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0
BURNING SENSATION	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Body as a whole - general disorders	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0
MEDICINE INEFFECTIVE	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
TUBERCULOSIS	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Platelet, bleeding & clotting disorders	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0
BRUISE	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0
Skin and appendages disorders	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0
NAIL DISORDER	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
RASH ERYTHEMATOUS	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Gastro-intestinal system disorders	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
CONSTIPATION	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Urinary system disorders	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Total	11 (1.62)	(0.67 , 2.57)	14	2 (0.29)	(0.00 , 0.70)	2

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	AE			ADR*		
	Incidence† n (%)	95% CI§ (Lower , Upper)	No. of AE	Incidence‡ n (%)	95% CI§ (Lower , Upper)	No. of AE

All subjects who enrolled this study: All patients except subjects who were enrolled by duplicate and didn't receive BOTOX and follow-up failure.

* ADR(Adverse Drug Reaction) : all AEs excluding the AEs whose causal relation with BOTOX is 'Unlikely'

† The percentage of 'Incidence of AE' = (No. subjects of AE/No. subjects who enrolled this study)*100%

‡ The percentage of 'Incidence of ADR' = (No. subjects of ADR/No. subjects who enrolled this study)*100%

§ 95% Confidence Interval for AE/ADR incidence is calculated using the normal approximation method.

Coding Dictionary : WHO-ART 092

B. Safety analysis set

During the surveillance period, 14 AEs were reported in 11 out of 667 subjects (1.65%) in the safety analysis set (Table 15).

When analyzing AEs by SOC, most common AEs included 'Application site disorders' and 'Central & peripheral nervous system disorders' in 0.45% each (3/667 subjects), followed by 'Body as a whole - general disorders', 'Platelet, bleeding & clotting disorders', and 'Skin and appendages disorders' in 0.30% each (2/667 subjects), and 'Gastro-intestinal system disorders' and 'Urinary system disorders' in 0.15% each (1/667 subjects) (Table 15).

In the detailed analysis of reported AEs, 'EYELID PTOSIS', 'INJECTION SITE PAIN' and 'BRUISE' occurred in 0.30 % each (2/667 subjects, 2 cases each), 'MEDICINE INEFFECTIVE', 'TUBERCULOSIS', 'BURNING SENSATION', 'INJECTION SITE SWELLING', 'NAIL DISORDER', 'RASH ERYTHEMATOUS', 'CONSTIPATION', and 'RENAL FAILURE ACUTE' occurred in 0.15% each (1/667 subjects, 1 case each) (Table 15).

Among these, 2 cases from 2 subjects (0.30%) were ADRs for which causal relationship to the study drug could not be excluded (Table 15).

The reported ADRs included 'INJECTION SITE PAIN' under "Application site disorders" in 0.30% (2/667 subjects, 2 cases) (Table 15).

Table 15. Incidence of AEs·ADRs (Safety analysis set)

	AE			ADR*		
	Incidence† n (%)	95% CI§ (Lower , Upper)	No. of AE	Incidence‡ n (%)	95% CI§ (Lower , Upper)	No. of AE
Application site disorders	3 (0.45)	(0.00 , 0.96)	3	2 (0.30)	(0.00 , 0.00)	2
INJECTION SITE PAIN	2 (0.30)	(0.00 , 0.71)	2	2 (0.30)	(0.00 , 0.00)	2
INJECTION SITE SWELLING	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Central & peripheral nervous system disorders	3 (0.45)	(0.00 , 0.96)	3	0 (0.00)	(0.00 , 0.00)	0
EYELID PTOSIS	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0
BURNING SENSATION	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Body as a whole - general disorders	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0
MEDICINE INEFFECTIVE	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0

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	AE			ADR*		
	Incidence† n (%)	95% CI§ (Lower , Upper)	No. of AE	Incidence‡ n (%)	95% CI§ (Lower , Upper)	No. of AE
TUBERCULOSIS	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Platelet, bleeding & clotting disorders	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0
BRUISE	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0
Skin and appendages disorders	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0
NAIL DISORDER	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
RASH ERYTHEMATOUS	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Gastro-intestinal system disorders	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
CONSTIPATION	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Urinary system disorders	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0
Total	11 (1.65)	(0.68 , 2.62)	14	2 (0.30)	(0.00 , 0.00)	2

* ADR(Adverse Drug Reaction) : all AEs excluding the AEs whose causal relation with BOTOX is 'Unlikely'

† The percentage of 'Incidence of AE' = (No. subjects of AE/No. subjects of safety analysis sets)*100%

‡ The percentage of 'Incidence of ADR' = (No. subjects of ADR/No. subjects of safety analysis sets)*100%

§ 95% Confidence Interval for AE/ADR incidence is calculated using the normal approximation method.

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C. Subjects excluded from the safety analysis set

During the surveillance period, no AEs were reported in the subjects excluded from the safety analysis set.

3.1.2 Serious adverse events·adverse drug reactions

A. Full analysis set

It was specified that any serious adverse events (SAEs) which occurred during the PMS period, should be reported irrespective of their causal relationship with the study drug, and any SAEs should be reported to Korea Institute of Drug Safety & Risk Management according to the procedure as soon as they are reported.

During the surveillance period, 1 SAE was reported in 1 out of 678 subjects (0.15%) in the full analysis set (Table 16).

1 SAE was 'RENAL FAILURE ACUTE' under "Urinary system disorders". There were no serious ADRs for which causal relationship to the study drug could not be excluded (Table 16).

Details of SAEs in the full analysis set are presented in the table below (Table 17).

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Table 16. Incidence of serious AEs·ADRs (Full analysis set)

	Serious AE			Serious ADR*		
	Incidence† n(%)	95% CI§ (Lower, Upper)	No. of AE	Incidence‡ n(%)	95% CI§ (Lower, Upper)	No. of AE
Urinary system disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Total	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0

All subjects who enrolled this study: All patients except subjects who were enrolled by duplicate and didn't receive BOTOX and follow-up failure.

* ADR(Adverse Drug Reaction) : all AEs excluding the AEs whose causal relation with BOTOX is 'Unlikely'

† The percentage or 'Incidence proportion of SAE' = (No. subjects of SAE/No. subjects who enrolled this study)*100%

‡ The percentage or 'Incidence proportion of SADR' = (No. subjects of SADR/No. subjects who enrolled this study)*100%

§ 95% Confidence Interval for SAE/SADR incidence is calculated using the normal approximation method.

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Table 17. Details of serious AEs·ADRs (Full analysis set)

caseno	SOC	AE	Onset Date	Stop Date	Seriousness Criteria	Severity	Current Status	Causal Relationship	Causal Relationship(Injection procedure)	Treatment received	Expected
[redacted]	Urinary system disorders	RENAL FAILURE ACUTE	[redacted]	[redacted]	Requires inpatient hospitalization or prolongs existing hospitalization	Mild	Resolved without sequelae	Unlikely	Unlikely	Yes	Unexpected AE

All subjects who enrolled in this study: All patients except subjects who were enrolled by duplicate and didn't receive BOTOX and follow-up failure.
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B. Safety analysis set

During the surveillance period, 1 SAE was reported in 1 out of 667 subjects (0.15%) in the safety analysis set (Table 18).

1 SAE was 'RENAL FAILURE ACUTE' under "Urinary system disorders". There were no serious ADRs for which causal relationship to the study drug could not be excluded (Table 18).

Details of SAEs in the safety analysis set are presented in the table below (Table 19).

Table 18. Incidence of serious AEs·ADRs (Safety analysis set)

	Serious AE			Serious ADR*		
	Incidence† n(%)	95% CI§ (Lower, Upper)	No. of AE	Incidence‡ n(%)	95% CI§ (Lower, Upper)	No. of AE
Urinary system disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Total	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0

* ADR(Adverse Drug Reaction) : all AEs excluding the AEs whose causal relation with BOTOX is 'Unlikely'
† The percentage or 'Incidence proportion of SAE' = (No. subjects with SAE/No. subjects of safety analysis sets)*100%
‡ The percentage or 'Incidence proportion of SADR' = (No. subjects with SADR/No. subjects of safety analysis sets)*100%
§ 95% Confidence Interval for SAE/SADR incidence is calculated using the normal approximation method.
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Table 19. Details of serious AEs·ADRs (Safety analysis set)

caseno	SOC	AE	Onset Date	Stop Date	Seriousness Criteria	Severity	Current Status	Causal Relationship	Causal Relationship(Injection procedure)	Treatment received	Expected
[redacted]	Urinary system disorders	RENAL FAILURE ACUTE	[redacted]	[redacted]	Requires inpatient hospitalization or prolongs existing hospitalization	Mild	Resolved without sequelae	Unlikely	Unlikely	Yes	Unexpected AE

Safety analysis set: The patients except subjects who were ‘Foreigners (not Korean)’, ‘Duplicate’, ‘didn’t receive BOTOX for this study’, ‘Follow-up failure’, and ‘Violated the usage/dosage’
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3.1.3 Unexpected adverse events·adverse drug reactions

A. Full analysis set

During the surveillance period, 4 unexpected AEs were reported in 3 out of 678 subjects (0.44%) in the full analysis set (Table 20).

In the detailed analysis of unexpected AEs, 'TUBERCULOSIS' under "Body as a whole - general disorders", 'BURNING SENSATION' under "Central & peripheral nervous system disorders", 'NAIL DISORDER' under "Skin and appendages disorders", and 'RENAL FAILURE ACUTE' under "Urinary system disorders" occurred in 0.15% each (1/678 subjects, 1 case) (Table 20).

Among these, there were no ADRs for which causal relationship to the study drug could not be excluded (Table 20).

Details of unexpected AEs in the full analysis set are presented in the table below (Table 21).

Table 20. Incidence of unexpected AEs·ADRs (Full analysis set)

	Unexpected AE			Unexpected ADR*		
	Incidence† n(%)	95% CI§ (Lower, Upper)	No. of AE	Incidence‡ n(%)	95% CI§ (Lower, Upper)	No. of AE
Body as a whole - general disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
TUBERCULOSIS	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Central & peripheral nervous system disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
BURNING SENSATION	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Skin and appendages disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
NAIL DISORDER	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Urinary system disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Total	3(0.44)	(0.00 , 0.94)	4	0(0.00)	(0.00 , 0.00)	0

All subjects who enrolled this study: All patients except subjects who were enrolled by duplicate and didn't receive BOTOX and follow-up failure.

* ADR(Adverse Drug Reaction) : all AEs excluding the AEs whose causal relation with BOTOX is 'Unlikely'

† The percentage or 'Incidence proportion of SAE' = (No. subjects of SAE/No. subjects who enrolled this study)*100%

‡ The percentage or 'Incidence proportion of SADR' = (No. subjects of SADR/No. subjects who enrolled this study)*100%

§ 95% Confidence Interval for SAE/SADR incidence is calculated using the normal approximation method.

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Table 21. Details of unexpected AEs·ADRs (Full analysis set)

caseno	SOC	AE	Onset Date	Stop Date	Serious	Severity	Current Status	Causal Relationship	Causal Relationship(Injection procedure)	Treatment received
[redacted]	Skin and appendages disorders	NAIL DISORDER	[redacted]	[redacted]	Non-serious	Mild	Resolved without sequelae	Unlikely	Unlikely	No
[redacted]	Body as a whole - general disorders	TUBERCULOSIS	[redacted]		Non-serious	Mild	Ongoing	Unlikely	Unlikely	No
[redacted]	Urinary system disorders	RENAL FAILURE ACUTE	[redacted]	[redacted]	Serious	Mild	Resolved without sequelae	Unlikely	Unlikely	Yes
[redacted]	Central & peripheral nervous system disorders	BURNING SENSATION	[redacted]	[redacted]	Non-serious	Mild	Resolved without sequelae	Unlikely	Unlikely	No

All subjects who enrolled this study: All patients except subjects who were enrolled by duplicate and didn't receive BOTOX and follow-up failure.

[redacted] "Tuberculosis" was reported by "latent tuberculosis".

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B. Safety analysis set

During the surveillance period, 4 unexpected AEs were reported in 3 out of 667 subjects (0.45%) in the safety analysis set (Table 22).

In the detailed analysis of unexpected AEs, 'TUBERCULOSIS' under "Body as a whole - general disorders", 'BURNING SENSATION' under "Central & peripheral nervous system disorders", 'NAIL DISORDER' under "Skin and appendages disorders", and 'RENAL FAILURE ACUTE' under "Urinary system disorders" occurred in 0.15% each (1/667 subjects, 1 case) (Table 22).

Among these, there were no ADRs for which causal relationship to the study drug could not be excluded (Table 22).

Details of unexpected AEs in the safety analysis set are presented in the table below (Table 23).

Table 22. Incidence of unexpected AEs·ADRs (Safety analysis set)

	Unexpected AE			Unexpected ADR*		
	Incidence† n(%)	95% CI§ (Lower, Upper)	No. of AE	Incidence‡ n(%)	95% CI§ (Lower, Upper)	No. of AE
Body as a whole - general disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
TUBERCULOSIS	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Central & peripheral nervous system disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
BURNING SENSATION	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Skin and appendages disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
NAIL DISORDER	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Urinary system disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Total	3(0.45)	(0.00 , 0.96)	4	0(0.00)	(0.00 , 0.00)	0

* ADR(Adverse Drug Reaction) : all AEs excluding the AEs whose causal relation with BOTOX is 'Unlikely'

† The percentage or 'Incidence proportion of SAE' = (No. subjects of SAE/No. subjects of safety analysis sets)*100%

‡ The percentage or 'Incidence proportion of SADR' = (No. subjects of SADR/No. subjects of safety analysis sets)*100%

§ 95% Confidence Interval for SAE/SADR incidence is calculated using the normal approximation method.

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Table 23. Details of unexpected AEs·ADRs (Safety analysis set)

caseno	SOC	AE	Onset Date	Stop Date	Serious	Severity	Current Status	Causal Relationship	Causal Relationship(Injection procedure)	Treatment received
[redacted]	Skin and appendages disorders	NAIL DISORDER	[redacted]	[redacted]	Non-serious	Mild	Resolved without sequelae	Unlikely	Unlikely	No
[redacted]	Body as a whole - general disorders	TUBERCULOSIS	[redacted]		Non-serious	Mild	Ongoing	Unlikely	Unlikely	No
[redacted]	Urinary system disorders	RENAL FAILURE ACUTE	[redacted]	[redacted]	Serious	Mild	Resolved without sequelae	Unlikely	Unlikely	Yes
[redacted]	Central & peripheral nervous system disorders	BURNING SENSATION	[redacted]	[redacted]	Non-serious	Mild	Resolved without sequelae	Unlikely	Unlikely	No

[redacted]) "Tuberculosis" was reported by "latent tuberculosis".
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3.1.4 Unexpected serious adverse events·adverse drug reactions

A. Full analysis set

During the surveillance period, 1 unexpected SAE was reported in 1 out of 678 subjects (0.15%) in the full analysis set (Table 24).

1 unexpected SAE was 'RENAL FAILURE ACUTE' under "Urinary system disorders". There were no unexpected serious ADRs for which causal relationship to the study drug could not be excluded (Table 24).

Details of unexpected SAEs in the full analysis set are presented in the table below (Table 25).

Table 24. Incidence of unexpected serious AEs·ADRs (Full analysis set)

	Unexpected Serious AE			Unexpected Serious ADR*		
	Incidence† n(%)	95% CI§ (Lower, Upper)	No. of AE	Incidence‡ n(%)	95% CI§ (Lower, Upper)	No. of AE
Urinary system disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Total	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0

All subjects who enrolled this study: All patients except subjects who were enrolled by duplicate and didn't receive BOTOX and follow-up failure.

* ADR(Adverse Drug Reaction) : all AEs excluding the AEs whose causal relation with BOTOX is 'Unlikely'

† The percentage or 'Incidence proportion of Unexpected Serious AE' = (No. subjects of Unexpected Serious AE/No. subjects who enrolled this study)*100%

‡ The percentage or 'Incidence proportion of Unexpected Serious ADR' = (No. subjects of Unexpected Serious ADR/No. subjects who enrolled this study)*100%

§ 95% Confidence Interval for Unexpected Serious AE/ADR incidence is calculated using the normal approximation method.

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Table 25. Details of unexpected serious AEs·ADRs (Full analysis set)

caseno	SOC	AE	Onset Date	Stop Date	Seriousness Criteria	Severity	Current Status	Causal Relationship	Causal Relationship(Injection procedure)	Treatment received
[redacted]	Urinary system disorders	RENAL FAILURE ACUTE	[redacted]	[redacted]	Requires inpatient hospitalization or prolongs existing hospitalization	Mild	Resolved without sequelae	Unlikely	Unlikely	Yes

All subjects who enrolled this study: All patients except subjects who were enrolled by duplicate and didn't receive BOTOX and follow-up failure.
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B. Safety analysis set

During the surveillance period, 1 unexpected serious AE was reported in 1 out of 667 subjects (0.15%) in the safety analysis set (Table 26).

One (1) unexpected SAE was 'RENAL FAILURE ACUTE' under "Urinary system disorders". There were no unexpected serious ADRs for which causal relationship to the study drug could not be excluded (Table 26).

Details of unexpected serious AEs in the safety analysis set are presented in the table below (Table 27).

Table 26. Incidence of unexpected serious AEs·ADRs (Safety analysis set)

	Serious AE			Serious ADR*		
	Incidence† n(%)	95% CI§ (Lower, Upper)	No. of AE	Incidence‡ n(%)	95% CI§ (Lower, Upper)	No. of AE
Urinary system disorders	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0
Total	1(0.15)	(0.00 , 0.44)	1	0(0.00)	(0.00 , 0.00)	0

* ADR(Adverse Drug Reaction) : all AEs excluding the AEs whose causal relation with BOTOX is 'Unlikely'

† The percentage or 'Incidence proportion of SAE' = (No. subjects of SAE/No. subjects of safety analysis sets)*100%

‡ The percentage or 'Incidence proportion of SADR' = (No. subjects of SADR/No. subjects of safety analysis sets)*100%

§ 95% Confidence Interval for SAE/SADR incidence is calculated using the normal approximation method.

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Table 27. Details of unexpected serious AEs·ADRs (Safety analysis set)

caseno	SOC	AE	Onset Date	Stop Date	Seriousness Criteria	Severity	Current Status	Causal Relationship	Causal Relationship(Injection procedure)	Treatment received
[redacted]	Urinary system disorders	RENAL FAILURE ACUTE	[redacted]	[redacted]	Requires inpatient hospitalization or prolongs existing hospitalization	Mild	Resolved without sequelae	Unlikely	Unlikely	Yes

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3.1.5 Classification of adverse events by severity

When classifying incidence proportion by the severity of the AEs in the full analysis set into 3 categories of 'Mild', 'Moderate', and 'Severe', 'Mild' accounted for 1.33% (9/678 subjects, 12 cases) and 'Moderate' and 'Severe' for 0.15% each (1/678 subjects, 1 case each) (Table 28).

When classifying incidence proportion by the severity of the AEs in the safety analysis set into 3 categories of 'Mild', 'Moderate', and 'Severe', 'Mild' accounted for 1.35% (9/667 subjects, 12 cases) and 'Moderate' and 'Severe' for 0.15% each (1/667 subjects, 1 case each) (Table 29).

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Table 28. Severity of AEs (Full analysis set)

	Mild			Moderate			Severe		
	Incidence* n (%)	95% CI† (Lower , Upper)	No. of AE	Incidence* n (%)	95% CI† (Lower , Upper)	No. of AE	Incidence* n (%)	95% CI† (Lower , Upper)	No. of AE
Application site disorders	3 (0.44)	(0.00 , 0.94)	3	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
INJECTION SITE PAIN	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
INJECTION SITE SWELLING	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Central & peripheral nervous system disorders	1 (0.15)	(0.00 , 0.44)	1	1 (0.15)	(0.00 , 0.44)	1	1 (0.15)	(0.00 , 0.44)	1
EYELID PTOSIS	0 (0.00)	(0.00 , 0.00)	0	1 (0.15)	(0.00 , 0.44)	1	1 (0.15)	(0.00 , 0.44)	1
BURNING SENSATION	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Body as a whole - general disorders	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
MEDICINE INEFFECTIVE	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
TUBERCULOSIS	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Platelet, bleeding & clotting disorders	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
BRUISE	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Skin and appendages disorders	2 (0.29)	(0.00 , 0.70)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
NAIL DISORDER	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
RASH ERYTHEMATOUS	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Gastro-intestinal system disorders	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
CONSTIPATION	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Urinary system disorders	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Total	9 (1.33)	(0.47 , 2.19)	12	1 (0.15)	(0.00 , 0.44)	1	1 (0.15)	(0.00 , 0.44)	1

All subjects who enrolled this study: All patients except subjects who were enrolled by duplicate and didn't receive BOTOX and follow-up failure.

† The percentage of 'Incidence of AE' = (No. subjects of AE/No. subjects who enrolled this study)*100%

§ 95% Confidence Interval for AE incidence is calculated using the normal approximation method.

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Table 29. Severity of AEs (Safety analysis set)

	Mild			Moderate			Severe		
	Incidence* n (%)	95% CI† (Lower , Upper)	No. of AE	Incidence* n (%)	95% CI† (Lower , Upper)	No. of AE	Incidence* n (%)	95% CI† (Lower , Upper)	No. of AE
Application site disorders	3 (0.45)	(0.00 , 0.96)	3	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
INJECTION SITE PAIN	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
INJECTION SITE SWELLING	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Central & peripheral nervous system disorders	1 (0.15)	(0.00 , 0.44)	1	1 (0.15)	(0.00 , 0.44)	1	1 (0.15)	(0.00 , 0.44)	1
EYELID PTOSIS	0 (0.00)	(0.00 , 0.00)	0	1 (0.15)	(0.00 , 0.44)	1	1 (0.15)	(0.00 , 0.44)	1
BURNING SENSATION	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Body as a whole - general disorders	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
MEDICINE INEFFECTIVE	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
TUBERCULOSIS	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Platelet, bleeding & clotting disorders	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
BRUISE	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Skin and appendages disorders	2 (0.30)	(0.00 , 0.71)	2	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
NAIL DISORDER	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
RASH ERYTHEMATOUS	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Gastro-intestinal system disorders	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
CONSTIPATION	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Urinary system disorders	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
RENAL FAILURE ACUTE	1 (0.15)	(0.00 , 0.44)	1	0 (0.00)	(0.00 , 0.00)	0	0 (0.00)	(0.00 , 0.00)	0
Total	9 (1.35)	(0.47 , 2.22)	12	1 (0.15)	(0.00 , 0.44)	1	1 (0.15)	(0.00 , 0.44)	1

* The percentage of 'Incidence of AE' = (No. subjects of AE/No. subjects of safety analysis sets)*100%

† 95% Confidence Interval for AE incidence is calculated using the normal approximation method.

Coding Dictionary : WHO-ART 092

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3.1.6 Tendency of other adverse events incidence

No subject was reported to have distant spread of toxic effects. Eyelid ptosis is considered to be the local effect which corresponds to the pharmacological characteristics of the study drug.

3.1.7 Incidence of adverse events by factor

A. Demographic chracteristics of the subjects

Incidence proportions of AEs analyzed by age was 2.56% (5/195 subjects, 7 cases) in '30 years ~ 39 years', 2.11% (3/142 subject, 3 cases) in '40 years ~ 49 years', 1.32% (2/151 subjects, 2 cases) in '20 years ~ 29 years', and 0.91% (1/110 subject, 2 cases) in '50 years ~ 59 years'. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=0.6955) (Table 30).

When subjects of '65 years or/and over' were classified as the elderly group, no AEs were reported in this group, and the incidence proportion of AEs was 1.74% (11/631 subjects, 14 cases) in subjects of 'below 65 years'. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=1.0000) (Table 30).

Incidence proportions of AEs analyzed by sex was 1.89% (11/582 subjects, 14 cases) in 'Female' subjects and no adverse events were reported in 'Male' subjects. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=0.3753) (Table 30).

There were no pregnant women among the female subjects and none of the subjects became pregnant after receiving the study drug (Table 30).

Incidence proportions of AEs analyzed by treatment indications was 3.48% (7/201 subjects, 7 cases) in 'moderate to severe crow's feet lines and glabellar lines when treated simultaneously' and 0.86% (4/466 subject, 7 cases) in 'moderate to severe lateral canthal lines (crow's feet lines) associated with orbicularis oculi activity'. The difference in the incidence proportions of AEs between the groups was statistically significant (p=0.0212) (Table 30).

Table 30. Incidence of AEs by demographic baseline data of the subjects (Safety analysis set)

		Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
Age	< 20 years	0(0.00)	(0.00, 0.00)	0	0(0.00)	0.6955 Fisher`s Exact test
	20 years ~ 29 years	2(1.32)	(0.00, 3.15)	2	151(22.64)	
	30 years ~ 39 years	5(2.56)	(0.35, 4.78)	7	195(29.24)	
	40 years ~ 49 years	3(2.11)	(0.00, 4.48)	3	142(21.29)	
	50 years ~ 59 years	1(0.91)	(0.00, 2.68)	2	110(16.49)	
	≥ 60 years	0(0.00)	(0.00, 0.00)	0	69(10.34)	
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
Elderly	below 65 years	11(1.74)	(0.72, 2.76)	14	631(94.60)	1.0000 Fisher`s Exact test
	65 years or/and over	0(0.00)	(0.00, 0.00)	0	36(5.40)	
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
Sex	Male	0(0.00)	(0.00, 0.00)	0	85(12.74)	0.3753 Fisher`s Exact test
	Female	11(1.89)	(0.78, 3.00)	14	582(87.26)	

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		Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
Currently pregnant§	Yes	0(0.00)	(0.00, 0.00)	0	0(0.00)	NA
	No	11(1.89)	(0.78, 3.00)	14	582(100.00)	
	Total	11(1.89)	(0.78, 3.00)	14	582(100.00)	
Pregnancy since the index BOTOX treatment§	Yes	0(0.00)	(0.00, 0.00)	0	0(0.00)	NA
	No	11(1.89)	(0.78, 3.00)	14	582(100.00)	
	Total	11(1.89)	(0.78, 3.00)	14	582(100.00)	
Treatment indication	moderate to severe lateral canthal lines associated with orbicularis oculi activity	4(0.86)	(0.02, 1.70)	7	466(69.87)	0.0212
	moderate to severe crow's feet lines and glabellar lines, when treated simultaneously	7(3.48)	(0.95, 6.02)	7	201(30.13)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	

* The percentage of 'Incidence of AE' = (No. of Subjects with AE in each category)/(No. of Subjects in each category)*100
† 95% Confidence Interval for adverse event incidence is calculated using the normal approximation method.
‡ The p-value is about that relation between Category and incidence of AEs
§ For female

B. Past treatment history

Incidence proportions of AEs analyzed by the history of facial aesthetic procedures (excluding the study drug) within the past 6 months was 6.35% (4/63 subjects, 4 cases) in subjects with the history of procedures and 1.16% (7/604 subjects, 10 cases) in subjects without the history of procedures. The difference in the incidence proportions of AEs between the groups was statistically significant (p=0.0144) (Table 31).

Incidence proportions of AEs analyzed by the history of other nontoxin or nonperiocular facial aesthetic or dermatologic treatment at baseline visit was 7.69% (5/65 subjects, 7 cases) in subjects with the history of treatment and 1.00% (6/602 subjects, 7 cases) in subjects without the history of treatment. The difference in the incidence proportions of AEs between the groups was statistically significant (p=0.0022) (Table 31).

Incidence proportions of AEs analyzed by the history of the study drug or other botulinum toxin use within the past 6 months was 3.19% (3/94 subjects, 3 cases) in subjects with the past treatment history and 1.40% (8/573 subjects, 11 cases) in subjects without the history. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=0.1929) (Table 31).

Table 31. Incidence of AEs by past treatment history (Safety analysis set)

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		Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
History of facial aesthetic procedure (excluding BOTOX) in the past 6 months	Yes	4(6.35)	(0.33, 12.37)	4	63(9.45)	0.0144
	No	7(1.16)	(0.31, 2.01)	10	604(90.55)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
Other nontoxin or nonperiocular facial aesthetic or dermatologic treatment at current visit	Yes	5(7.69)	(1.21, 14.17)	7	65(9.75)	0.0022
	None	6(1.00)	(0.20, 1.79)	7	602(90.25)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
Past BOTOX or other botulinum toxin in the past 6 months	Yes	3(3.19)	(0.00, 6.74)	3	94(14.09)	0.1929
	None	8(1.40)	(0.44, 2.36)	11	573(85.91)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	

* The percentage of 'Incidence of AE' = (No. of Subjects with AE in each category)/(No. of Subjects in each category)*100
† 95% Confidence Interval for adverse event incidence is calculated using the normal approximation method.
‡ The p-value is about that relation between Category and incidence of AEs

C. Medical history

Incidence proportions of AEs analyzed by other medical history including surgeries and complications of underlying diseases was 4.29% (3/70 subjects, 5 cases) in subjects with the medical history and 1.34% (8/597 subjects, 9 cases) in subjects without the medical history. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=0.0988) (Table 32).

Analyzing the incidence proportions of AEs by the detailed medical history of the subjects, allowing overlapped counting, 25.00% (2/8 subjects, 4 cases) had ‘Diseases of the circulatory system’, 20.00% (1/5 subjects, 3 cases) had ‘Certain infectious and parasitic diseases’, and 7.14% (1/14 subjects, 1 case) had ‘Factors influencing health status and contact with health services’ (Table 32).

Analyzing the incidence proportions of AEs by history of allergies, no AEs were reported in the subjects with history of allegies and 1.70% (11/647 subjects, 14 cases) reported AEs in the subjects without history of allegies. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=1.0000) (Table 32).

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Table 32. Incidence of AEs by medical history (Safety analysis set)

		Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
Medical History, Including Surgeries and Complications of Underlying Diseases§	Yes	3(4.29)	(0.00, 9.03)	5	70(10.49)	0.0988
	None	8(1.34)	(0.42, 2.26)	9	597(89.51)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
	Details for Medical History by dictionary (Overlappedǁ)					
	Diseases of the eye and adnexa	0(0.00)	(0.00, 0.00)	0	18(25.71)	
	Endocrine, nutritional and metabolic diseases	0(0.00)	(0.00, 0.00)	0	13(18.57)	
	Factors influencing health status and contact with health services	1(7.14)	(0.00, 20.63)	1	14(20.00)	
	Diseases of the musculoskeletal system and connective tissue	0(0.00)	(0.00, 0.00)	0	11(15.71)	
	Diseases of the circulatory system	0(0.00)	(0.00, 0.00)	0	7(10.00)	
	Diseases of the skin and subcutaneous tissue	2(25.00)	(0.00, 55.01)	4	8(11.43)	
	Diseases of the respiratory system	0(0.00)	(0.00, 0.00)	0	8(11.43)	
	Neoplasms	0(0.00)	(0.00, 0.00)	0	7(10.00)	
	Diseases of the digestive system	0(0.00)	(0.00, 0.00)	0	7(10.00)	
	Certain infectious and parasitic diseases	1(20.00)	(0.00, 55.06)	3	5(7.14)	
	Diseases of the genitourinary system	0(0.00)	(0.00, 0.00)	0	3(4.29)	
	Diseases of the nervous system	0(0.00)	(0.00, 0.00)	0	2(2.86)	
	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	0(0.00)	(0.00, 0.00)	0	1(1.43)	
	Injury, poisoning and certain other consequences of external causes	0(0.00)	(0.00, 0.00)	0	1(1.43)	
	Mental and behavioural disorders	0(0.00)	(0.00, 0.00)	0	1(1.43)	
History of Allergies	Yes	0(0.00)	(0.00, 0.00)	0	20(3.00)	1.0000 Fisher`s Exact test
	None	11(1.70)	(0.70, 2.70)	14	647(97.00)	
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	

* The percentage of 'Incidence of AE' = (No. of Subjects with AE in each category)/(No. of Subjects in each category)*100
† 95% Confidence Interval for adverse event incidence is calculated using the normal approximation method.
‡ The p-value is about that relation between Category and incidence of AEs
ǁ The same subject may appear in different categories
Dictionary: KCD

D. Concomitant medications

Incidence proportions of AEs analyzed by the presence of concomitant medications and other botulinum toxins except the study drug was 5.36% (3/56 subjects, 6 cases) in subjects with the history of concomitant medications and 1.31% (8/611 subjects, 8 cases) in subjects without the history of concomitant medications. The difference in the incidence proportions of AEs between

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the groups was not statistically significant (p=0.0570) (Table 33).
Analyzing the incidence proportions of AEs by the types of concomitant medications, allowing overlapped counting, 66.67% (2/3 subjects, 4 cases) had 'Dermatologicals', 33.33% (1/3 subjects, 1 case) had 'Eye', and 28.57% (2/7 subjects, 4 cases) had 'Allergy & Immune System' (Table 33).

Table 33. Incidence of AEs by concomitant medication (Safety analysis set)

	Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
Yes	3(5.36)	(0.00, 11.25)	6	56(8.40)	0.0570 Fisher`s Exact test
None	8(1.31)	(0.41, 2.21)	8	611(91.60)	
Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
Details for Concomitant Medication by dictionary (Overlapped§)					
Cardiovascular & Hematopoietic System	1(8.33)	(0.00, 23.97)	2	12(21.43)	
Anticoagulants, Antiplatelets & Fibrinolytics (Thrombolytics)	0(0.00)	(0.00, 0.00)	0	3(5.36)	
Diuretics	1(33.33)	(0.00, 86.68)	2	3(5.36)	
Dyslipidaemic Agents	0(0.00)	(0.00, 0.00)	0	3(5.36)	
Other Antihypertensives	0(0.00)	(0.00, 0.00)	0	3(5.36)	
Angiotensin Ⅱ Antagonists	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Beta-Blockers	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Phlebitis & Varicose Preparations	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Gastrointestinal & Hepatobiliary System	1(6.67)	(0.00, 19.29)	2	15(26.79)	
Antacids, Antireflux Agents & Antiulcerants	0(0.00)	(0.00, 0.00)	0	9(16.07)	
GIT Regulators, Antiflatulents & Anti-inflammatories	0(0.00)	(0.00, 0.00)	0	3(5.36)	
Cholagogues, Cholelitholytics & Hepatic Protectors	1(50.00)	(0.00, 100.00)	2	2(3.57)	
Digestives	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Laxatives, Purgatives	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Musculo-Skeletal System	0(0.00)	(0.00, 0.00)	0	15(26.79)	
Muscle Relaxants	0(0.00)	(0.00, 0.00)	0	12(21.43)	
Other Drugs Acting on the Musculo-Skeletal System	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Disease-Modifying Anti-Rheumatic Drugs (DMARDs)	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Anti-infectives (systemic)	2(20.00)	(0.00, 44.79)	5	10(17.86)	
Cephalosporins	0(0.00)	(0.00, 0.00)	0	3(5.36)	
Tetracyclines	0(0.00)	(0.00, 0.00)	0	3(5.36)	
Anti-TB Agents	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Antibacterial Combinations	1(100.00)	(100.00, 100.00)	2	1(1.79)	
Antifungals	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Antivirals	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Macrolides	1(100.00)	(100.00, 100.00)	3	1(1.79)	
Central Nervous System	0(0.00)	(0.00, 0.00)	0	10(17.86)	
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	0(0.00)	(0.00, 0.00)	0	7(12.50)	
Analgesics (Non-Opioid) & Antipyretics	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Drugs For Neuropathic Pain	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Hypnotics & Sedatives	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Endocrine & Metabolic System	0(0.00)	(0.00, 0.00)	0	9(16.07)	
Thyroid Hormones	0(0.00)	(0.00, 0.00)	0	5(8.93)	
Antidiabetic Agents	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Other Agents Affecting Metabolism	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Anti-obesity Agents	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Antithyroid Agents	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Allergy & Immune System	2(28.57)	(0.00, 62.04)	4	7(12.50)	
Antihistamines & Antiallergics	2(28.57)	(0.00, 62.04)	4	7(12.50)	
Vitamins & Minerals	0(0.00)	(0.00, 0.00)	0	6(10.71)	
Calcium / with Vitamins	0(0.00)	(0.00, 0.00)	0	5(8.93)	

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	Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
Vitamins & Minerals (Pre & Post Natal) / Antianemics	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Vitamins A, D & E	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Hormones	1(20.00)	(0.00, 55.06)	2	5(8.93)	
Corticosteroid Hormones	1(25.00)	(0.00, 67.44)	2	4(7.14)	
Oestrogens & Progesterones & Related Synthetic Drugs	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Dermatologicals	2(66.67)	(13.32, 100.00)	4	3(5.36)	
Acne Treatment Preparations	2(66.67)	(13.32, 100.00)	4	3(5.36)	
Eye	1(33.33)	(0.00, 86.68)	1	3(5.36)	
Eye Corticosteroids	1(50.00)	(0.00, 100.00)	1	2(3.57)	
Ophthalmic Lubricants	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Oncology	0(0.00)	(0.00, 0.00)	0	3(5.36)	
Hormonal Chemotherapy	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Cytotoxic Chemotherapy	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Respiratory System	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Antiasthmatic & COPD Preparations	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Cough & Cold Preparations	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Genito-Urinary System	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Drugs for Erectile Dysfunction and Ejaculatory Disorders	0(0.00)	(0.00, 0.00)	0	1(1.79)	
Miscellaneous	0(0.00)	(0.00, 0.00)	0	2(3.57)	
Miscellaneous	0(0.00)	(0.00, 0.00)	0	2(3.57)	

* The percentage of 'Incidence of AE' = (No. of Subjects with AE in each category)/(No. of Subjects in each category)*100
† 95% Confidence Interval for adverse event incidence is calculated using the normal approximation method.
‡ The p-value is about that relation between Category and incidence of AEs
§ The same subject may appear in different categories
Dictionary: KIMS

E. Special populations

Among the special population groups, the analysis result of elderly subjects (≤ 65 years) was presented in Table 30.

Incidence proportions of AEs analyzed by the presence of renal impairment was none in subjects with renal impairment and 1.65% (11/666 subjects, 14 cases) in subject without renal impairment. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=1.0000) (Table 34).

Incidence proportions of AEs analyzed by the presence of hepatic impairment was none in subjects with hepatic impairment and 1.65% (11/666 subjects, 14 cases) in subject without hepatic impairment. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=1.0000) (Table 34).

Table 34. Incidence of AEs in special populations (Safety analysis set)

		Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
Renal impairment	Yes	0(0.00)	(0.00, 0.00)	0	1(0.15)	1.0000 Fisher`s Exact test
	No	11(1.65)	(0.68, 2.62)	14	666(99.85)	
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	

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		Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
Hepatic impairment	Yes	0(0.00)	(0.00, 0.00)	0	1(0.15)	1.0000
	No	11(1.65)	(0.68, 2.62)	14	666(99.85)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	

* The percentage of 'Incidence of AE' = (No. of Subjects with AE in each category)/(No. of Subjects in each category)*100
† 95% Confidence Interval for adverse event incidence is calculated using the normal approximation method.
‡ The p-value is about that relation between Category and incidence of AEs

F. Information related to the study drug injection

All subjects who had treatment indication for lateral canthal lines were administered the study drug in '6 injection sites' with '24 units' and all subjects who had treatment indication for lateral canthal lines and glabellar lines treatment simultaneously were administered the study drug in '6 + 5 sites' with '24 + 20 units'. Therefore, incidence proportion of AEs was identical with the incidence proportions of AEs per each indication in the safety analysis set. The difference in the incidence proportions of AEs between the groups was statistically significant (p=0.0212) (Table 35).

Incidence proportions of AEs were analyzed by the additional treatment of the study drug. No AEs were reported in subjects who received the additional dose of the study drug after the administration of the study drug and 1.65% (11/665 subjects, 14 cases) reported AEs in subjects who didn't receive the additional dose of the study drug. The difference in the incidence proportions of AEs between the groups was not statistically significant (p=1.0000) (Table 35).

Table 35. Incidence of AEs by the information related to the study drug injection (Safety analysis set)

		Incidence* n(%)	95% CI† (Lower, Upper)	No. of AE	Total n(%)	p-value‡
Number of injection sites	6 sites(Crow's feet lines)	4(0.86)	(0.02, 1.70)	7	466(69.87)	0.0212
	6+5 sites(Glabellar lines if treated simultaneously with crow's feet lines)	7(3.48)	(0.95, 6.02)	7	201(30.13)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
Total units injected	24 units(Crow's feet lines)	4(0.86)	(0.02, 1.70)	7	466(69.87)	0.0212
	24+20 units(Glabellar lines if treated simultaneously with crow's feet lines)	7(3.48)	(0.95, 6.02)	7	201(30.13)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	
Received additional BOTOX treatment since the index BOTOX treatment	Yes	0(0.00)	(0.00, 0.00)	0	2(0.30)	1.0000
	No	11(1.65)	(0.68, 2.62)	14	665(99.70)	Fisher`s Exact test
	Total	11(1.65)	(0.68, 2.62)	14	667(100.00)	

* The percentage of 'Incidence of AE' = (No. of Subjects with AE in each category)/(No. of Subjects in each category)*100
† 95% Confidence Interval for adverse event incidence is calculated using the normal approximation method.
‡ The p-value is about that relation between Category and incidence of AEs

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G. Factors considered to affect the safety

Regarding the safety in this PMS, incidence of AEs was investigated by age, sex, pregnancy status, treatment indications, past treatment history, medical history, history of allergies, concomitant medications, and information related to the study drug injection as well as in special populations such as the elderly, subjects with renal impairment, and subjects with hepatic impairment.

The investigation results showed statistically significant difference in proportions AE incidence with 4 factors of treatment indications (p=0.0212), history of facial aesthetic procedures (excluding the study drug) within the past 6 months (p=0.0144), history of other nontoxin or nonperiocular facial aesthetic or dermatologic treatment (p=0.0022), and information related to the study drug injection (p=0.0212).

Incidence proportions of AEs analyzed by treatment indications was 3.48% (7/201 subjects, 7 cases) in 'moderate to severe crow's feet lines and glabellar lines when treated simultaneously' and 0.86% (4/466 subject, 7 cases) in 'moderate to severe lateral canthal lines (crow's feet lines) associated with orbicularis oculi activity'. The difference in the incidence proportions of AEs between the groups was statistically significant (p=0.0212).

According to the doses for respective indications in Korean product label information, all subjects who had treatment indication for lateral canthal lines were administered the study drug in '6 injection sites' with '24 units' and all subjects who had treatment indication for lateral canthal lines and glabellar lines treatment simultaneously, were administered the study drug in '6 + 5 sites' with '24 + 20 units'. Therefore, incidence proportion of AEs was identical with the incidence proportions of AEs per each indication. The difference in the incidence proportions of AEs between the groups was statistically significant (p=0.0212).

It seems that the tendency of this study is presented similar results found in previous clinical trial for each indication (glabellar lines treatment solely and crow's feet lines treatment solely). In the previous clilnical trials, the AE incidence proportions of glabella line treatment is higher than that of crow's feet lines. Since glabellar lines were treated with the crow's feet lines simultaneously in this surveillance, it seems that the AE incidence proportion of glabellar lines affected to statistical difference significantly. However despite the result is statistically significant, it is difficult to determine the medical and pharmaceutical significance based on this data alone.

Incidence proportions of AEs analyzed by the history of facial aesthetic procedures (excluding the study drug) within the past 6 months was 6.35% (4/63 subjects, 4 cases) in subjects with the history of procedures and 1.16% (7/604 subjects, 10 cases) in subjects without the history of procedures. The difference in the incidence proportions of AEs between the groups was statistically significant (p=0.0144).

Incidence proportions of AEs analyzed by the history of other nontoxin or nonperiocular facial aesthetic or dermatologic treatment at baseline visit was 7.69% (5/65 subjects, 7 cases) in subjects with the history of treatment and 1.00% (6/602 subjects, 7 cases) in subjects without the history of treatment. The difference in the incidence proportions of AEs between the groups was statistically significant (p=0.0022).

It seems that the results were affected the 'underlying conditions' of subjects who had a history of other nontoxin or nonperiocular facial aesthetic or dermatologic treatment. However despite the results of all 2 factors are statistically significant, and considering that PMS is non-

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interventional study, it is difficult to determine the medical and pharmaceutical significance based on this data alone.

Therefore, continued observation is deemed necessary for the above factors which showed statistically significant differences.

3.1.8 Detailed classification of adverse events

A total of 14 AE cases that were reported in the safety analysis set were classified based on the severity, outcome, causal relationship to the study drug/the injection procedure, and treatment received (Table 36).

When classifying the severity of the AEs into 3 categories of 'Mild', 'Moderate', and 'Severe', there were 12 'Mild' cases, 1 'Moderate' case, and 1 'Severe' case (Table 36).

When classifying the outcomes of AEs into 4 categories of 'Ongoing', 'Resolved without sequelae adverse event', 'Resolved with sequelae adverse event', and 'Death', there were 3 cases of 'Ongoing' and 11 cases of 'Resolved without sequelae adverse event' (Table 36).

When classifying the causal relationships of AE incidences to the study drug into 6 categories of 'Certain', 'Probable/likely', 'Possible', 'Unlikely', 'Conditional/unclassified', and 'Nonassessable/unclassifiable', there were 12 cases of 'Unlikely', 2 cases of 'Possible' (Table 36).

When classifying the causal relationships of AE incidences to the injection procedure of the study drug into 6 categories of 'Certain', 'Probable/likely', 'Possible', 'Unlikely', 'Conditional/unclassified', and 'Nonassessable/unclassifiable', there were 12 cases of 'Unlikely', 2 cases of 'Possible' (Table 36).

When classifying the presences of treatment after AE incidence into 2 categories of 'Yes' and 'No', There were 3 cases of 'Yes' and 11 cases of 'No' (Table 36).

The treatments for AEs were 'hospitalized and treated with antibiotics and steroid' to 'RENAL FAILURE ACUTE' and 'steroid eye drop (Predforte) use after medical examination of the ophthalmology', and 'implementation of high frequency procedure for alleviation of symptoms in frontalis and eyelid elevator' to 'EYELID PTOSIS'.

Table 36. Detailed classification of AEs (Safety analysis set)

		No. of AE
Severity	Mild	12
	Moderate	1
	Severe	1
Current Status*	Ongoing	3
	Resolved without sequelae adverse event	11
	Resolved with sequelae adverse event	0
	Death	0
Causal Relationship	Certain	0
	Probable/Likely	0
	Possible	2
	Unlikely	12

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		No. of AE
	Conditional/Unclassified	0
	Unassessable/Unclassifiable	0
Causal Relationship(Injection procedure)	Certain	0
	Probable/Likely	0
	Possible	2
	Unlikely	12
	Conditional/Unclassified	0
	Unassessable/Unclassifiable	0
Treatment received	Yes	3
	No	11
Total		14

* Based on last follow-up date

A. Severity of adverse events

Classification of AEs by severity is presented in the table below (Table 37).

Table 37. Classification of AEs by severity (Safety analysis set)

	Mild	Moderate	Severe	Total
Application site disorders	3	0	0	3
INJECTION SITE PAIN	2	0	0	2
INJECTION SITE SWELLING	1	0	0	1
Central & peripheral nervous system disorders	1	1	1	3
EYELID PTOSIS(눈꺼풀처짐)	0	1	1	2
BURNING SENSATION(작열감)	1	0	0	1
Body as a whole - general disorders	2	0	0	2
MEDICINE INEFFECTIVE	1	0	0	1
TUBERCULOSIS	1	0	0	1
Platelet, bleeding & clotting disorders	2	0	0	2
BRUISE	2	0	0	2
Skin and appendages disorders	2	0	0	2
NAIL DISORDER	1	0	0	1
RASH ERYTHEMATOUS	1	0	0	1
Gastro-intestinal system disorders	1	0	0	1
CONSTIPATION	1	0	0	1
Urinary system disorders	1	0	0	1
RENAL FAILURE ACUTE	1	0	0	1
Total	12	1	1	14

Coding Dictionary : WHO-ART 092

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B. Outcome of adverse events

Classification of AEs by outcome is presented in the table below (Table 38).

Table 38. Classification of AEs by outcome* (Safety analysis set)

	Ongoing	Resolved without sequelae adverse event	Resolved with sequelae adverse event	Death	Total
Application site disorders	1	2	0	0	3
INJECTION SITE PAIN	1	1	0	0	2
INJECTION SITE SWELLING	0	1	0	0	1
Central & peripheral nervous system disorders	0	3	0	0	3
EYELID PTOSIS	0	2	0	0	2
BURNING SENSATION	0	1	0	0	1
Body as a whole - general disorders	2	0	0	0	2
MEDICINE INEFFECTIVE	1	0	0	0	1
TUBERCULOSIS	1	0	0	0	1
Platelet, bleeding & clotting disorders	0	2	0	0	2
BRUISE	0	2	0	0	2
Skin and appendages disorders	0	2	0	0	2
NAIL DISORDER	0	1	0	0	1
RASH ERYTHEMATOUS	0	1	0	0	1
Gastro-intestinal system disorders	0	1	0	0	1
CONSTIPATION	0	1	0	0	1
Urinary system disorders	0	1	0	0	1
RENAL FAILURE ACUTE	0	1	0	0	1
Total	3	11	0	0	14

Coding Dictionary : WHO-ART 092

C. Classification of AEs by causal relationship to the study drug

Classification of AEs by causal relationship to the study drug is presented in the table below (Table 39).

Table 39. Classification of AEs by causal relationship to the study drug (Safety analysis set)

	Certain	Probable/ Likely	Possible	Unlikely	Conditional/ Unclassified	Unassessable/ Unclassifiable	Total
Application site disorders	0	0	2	1	0	0	3
INJECTION SITE PAIN	0	0	2	0	0	0	2
INJECTION SITE SWELLING	0	0	0	1	0	0	1
Central & peripheral nervous system disorders	0	0	0	3	0	0	3
EYELID PTOSIS	0	0	0	2	0	0	2
BURNING SENSATION	0	0	0	1	0	0	1
Body as a whole - general disorders	0	0	0	2	0	0	2
MEDICINE INEFFECTIVE	0	0	0	1	0	0	1
TUBERCULOSIS	0	0	0	1	0	0	1

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	Certain	Probable/ Likely	Possible	Unlikely	Conditional/ Unclassified	Unassessable/ Unclassifiable	Total
Platelet, bleeding & clotting disorders	0	0	0	2	0	0	2
BRUISE	0	0	0	2	0	0	2
Skin and appendages disorders	0	0	0	2	0	0	2
NAIL DISORDER	0	0	0	1	0	0	1
RASH ERYTHEMATOUS	0	0	0	1	0	0	1
Gastro-intestinal system disorders	0	0	0	1	0	0	1
CONSTIPATION	0	0	0	1	0	0	1
Urinary system disorders	0	0	0	1	0	0	1
RENAL FAILURE ACUTE	0	0	0	1	0	0	1
Total	0	0	2	12	0	0	14

Coding Dictionary : WHO-ART 092

D. Classification of AEs by causal relationship to the injection procedure of the study drug

Classification of AEs by causal relationship to the injection procedure of the study drug is presented in the table below (Table 40).

Table 40. Classification of AEs by causal relationship to the injection procedure of the study drug (Safety analysis set)

	Certain	Probable/ Likely	Possible	Unlikely	Conditional/ Unclassified	Unassessable/ Unclassifiable	Total
Application site disorders	0	0	2	1	0	0	3
INJECTION SITE PAIN	0	0	2	0	0	0	2
INJECTION SITE SWELLING	0	0	0	1	0	0	1
Central & peripheral nervous system disorders	0	0	0	3	0	0	3
EYELID PTOSIS	0	0	0	2	0	0	2
BURNING SENSATION	0	0	0	1	0	0	1
Body as a whole - general disorders	0	0	0	2	0	0	2
MEDICINE INEFFECTIVE	0	0	0	1	0	0	1
TUBERCULOSIS	0	0	0	1	0	0	1
Platelet, bleeding & clotting disorders	0	0	0	2	0	0	2
BRUISE	0	0	0	2	0	0	2
Skin and appendages disorders	0	0	0	2	0	0	2
NAIL DISORDER	0	0	0	1	0	0	1
RASH ERYTHEMATOUS	0	0	0	1	0	0	1
Gastro-intestinal system disorders	0	0	0	1	0	0	1
CONSTIPATION	0	0	0	1	0	0	1
Urinary system disorders	0	0	0	1	0	0	1
RENAL FAILURE ACUTE	0	0	0	1	0	0	1
Total	0	0	2	12	0	0	14

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E. AE treatment

Classification of AEs by the AE treatment is presented in the table below (Table 41).

Table 41. Classification of AEs by the AE treatment (Safety analysis set)

	Yes	No	Total
Application site disorders	0	3	3
INJECTION SITE PAIN	0	2	2
INJECTION SITE SWELLING	0	1	1
Central & peripheral nervous system disorders	2	1	3
EYELID PTOSIS	2	0	2
BURNING SENSATION	0	1	1
Body as a whole - general disorders	0	2	2
MEDICINE INEFFECTIVE	0	1	1
TUBERCULOSIS	0	1	1
Platelet, bleeding & clotting disorders	0	2	2
BRUISE	0	2	2
Skin and appendages disorders	0	2	2
NAIL DISORDER	0	1	1
RASH ERYTHEMATOUS	0	1	1
Gastro-intestinal system disorders	0	1	1
CONSTIPATION	0	1	1
Urinary system disorders	1	0	1
RENAL FAILURE ACUTE	1	0	1
Total	3	11	14

Coding Dictionary : WHO-ART 092

3.2 Effectiveness Data

Among the 667 subjects in the safety analysis set, 376 subjects were included in the effectiveness analysis set after excluding 277 subjects with ‘Missing information of overall assessment of change in crow’s feet lines by the investigator’, 1 subject who ‘receive a subsequent BOTOX injection before overall assessment of change in crow’s feet lines by the investigator’, and 13 subjects who were ‘collected effectiveness evaluations beyond 3 months after the index BOTOX injection’.

3.2.1 Results of effectiveness evaluation

Effectiveness evaluation was conducted through follow-up visit within 3 months after the study drug treatment or before receiving a subsequent study drug treatment (if one occurs prior to 3 months after the study drug injection). The overall improvement in lateral canthal lines was evaluated by the investigators with the 4 categories of ‘Improved’, ‘Unchanged’, ‘Worsened’, and ‘Not assessed’. The subjects classified as ‘Not assessed’ were excluded from the analysis.

The result of overall evaluation of changes in lateral canthal lines for 376 subjects in the effectiveness analysis set conducted by the investigators showed that 99.73% (375/376 subjects)

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was evaluated as ‘Improved’ and 0.27% (1/376 subjects) was ‘Unchanged’ (Table 42).

Table 42. Overall evaluation based on change in lateral canthal lines (Effectiveness analysis set)

	Total n (%)
Improved	375 (99.73)
Unchanged	1 (0.27)
Worsened	0 (0.00)
Total	376 (100.00)

In the effectiveness evaluation criteria, ‘Improved’ was considered as “Effectiveness” and ‘Unchanged’ and ‘Worsened’ were considered as “Ineffectiveness”. The study drug was found to be ‘effective’ in 99.73% (375/376 subjects) and ‘ineffective’ in 0.27% (1/376 subjects) (Table 43).

Table 43. Effectiveness evaluation results (Effectiveness analysis set)

Effectiveness* n (%)	95% CI† (Lower , Upper)	Ineffectiveness‡ n (%)	Total n (%)
375 (99.73)	(99.21 , 100.00)	1 (0.27)	376 (100.00)

* Overall assessment of change in crow's feet lines by the investigator is 'Improved'.

† 95% Confidence Interval for effectiveness is calculated using the normal approximation method.

‡ Overall assessment of change in crow's feet lines by the investigator is 'Unchanged' or 'Worsened'.

3.2.2 Effectiveness evaluation by factor

Among the 376 subjects in the effectiveness analysis set, the study drug was found to ‘effective’ in 375 subjects excluding 1 subject. Therefore the effectiveness rate was 99.73% (375/376 subjects) and analysis on effectiveness by specific factor was not conducted.

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Ⅳ. Results Other than PMS

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4. Results other than PMS

AEs collected from sources other than the PMS (through spontaneous reports, clinical studies, literature reports, etc.) during this PMS period are as follows. The AEs are detailed in Appendix 4 and 5 of this re-examination report and AE names have been coded using WHO-ART 092. Excluding those classified as having an 'Unlikely' causal relationship with the study drug, all AEs were classified as ADRs for which causal relationships with the study drug could not be ruled out.

4.1 AEs·ADRs (Other than PMS)

During this surveillance period, 23 AEs were collected in Korea from sources other than PMS.

In the detailed AEs, 5 events occurred in 'INJECTION SITE PAIN' caused by using other than indications, 3 events occurred each in 'INJECTION SITE ERYTHEMA' and 'INJECTION SITE PRURITUS'. All of these were ADRs for which causal relationship to the study drug could not be excluded (Table 44).

Table 44. Incidence of AEs·ADRs (Other thanPMS)

	Number of AEs	Number of ADRs
CHEST DISCOMFORT	2	2
DIZZINESS	1	1
INJECTION SITE BURNING	1	1
INJECTION SITE ERYTHEMA	3	3
INJECTION SITE PAIN	5	5
INJECTION SITE PRURITUS	3	3
INJECTION SITE SWELLING	1	1
MEDICINE INEFFECTIVE	2	2
OEDEMA	1	1
OPHTHALMOPLEGIA	1	1
PAIN	1	1
PARALYSIS FACIAL	1	1
RHABDOMYOSARCOMA	1	1
Total	23	23

Coding Dictionary : WHO-ART 092

4.2 Serious AEs·ADRs (Other than PMS)

During this surveillance period, 1 SAE 'RHABDOMYOSARCOMA' was collected in Korea from sources other than PMS. It was SADR for which causal relationship to the study drug could not be excluded (Table 45).

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Table 45. Incidence of serious AEs·ADRs (Other than PMS)

	Number of SAEs	Number of SADRs
RHABDOMYOSARCOMA	1	1
Total	1	1

Coding Dictionary : WHO-ART 092

4.3 Unexpected AEs·ADRs (Other than PMS)

During this surveillance period, 5 unexpected AEs were collected in Korea from sources other than PMS.

2 events occurred in 'CHEST DISCOMFORT', 1 events occurred each in 'OEDEMA', 'PAIN' and 'RHABDOMYOSARCOMA'. All of these were unexpected ADRs for which causal relationship to the study drug could not be excluded (Table 46).

Table 46. Incidence of unexpected AEs·ADRs (Other than PMS)

	Number of Unexpected AEs	Number of Unexpected ADRs
CHEST DISCOMFORT	2	2
OEDEMA	1	1
PAIN	1	1
RHABDOMYOSARCOMA	1	1
Total	5	5

Coding Dictionary : WHO-ART 092

4.4 Unexpected Serious AEs·ADRs (Other than PMS)

During this surveillance period, 1 unexpected SAE 'RHABDOMYOSARCOMA' was collected in Korea from sources other than PMS. It was unexpected SADR for which causal relationship to the study drug could not be excluded (Table 47).

Table 47. Incidence of unexpected serious AEs·ADRs (Other than PMS)

	Number of Unexpected SAEs	Number of Unexpected SADRs
RHABDOMYOSARCOMA	1	1
Total	1	1

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V. List of Adverse Events

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5. List of Adverse Events

[Appendix 3-1] Summary Tabulation of Adverse Drug Reactions in Post Marketing Surveillance

[Appendix 3-2] Summary Tabulation of Serious Adverse Events·Adverse Drug Reactions in Post Marketing Surveillance·Special Surveillance·Post Marketing Clinical Study

[Appendix 4] Summary Tabulation of Adverse Event Incidence Status

[Appendix 5] Table of Adverse Event Case Reports

[Appendix 7] Line-listing of Serious Adverse Events·Adverse Drug Reactions and Unexpected Adverse Drug Reactions

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Ⅵ. Discussions on Surveillance Results and Future Actions

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6. Discussions on Surveillance Results and Future Actions

During this re-examination period, CRFs of 695 subjects were retrieved by 26 investigators at 26 institutions. Among the subjects whose CRFs were retrieved, a total of 667 subjects were included in the safety analysis set after excluding 10 subjects who were 'Foreigners (not Korean)', 1 subject who was 'Duplicate', 5 subjects who 'didn't receive BOTOX for this study', 11 subjects of 'Follow-up failure', and 1 subject who 'Violated the usage/dosage'. Of these, 376 subjects were included in the effectiveness analysis set after excluding 277 subjects with 'Missing information of overall assessment of change in crow's feet lines by the investigator', 1 subject who 'receive a subsequent BOTOX injection before overall assessment of change in crow's feet lines by the investigator', and 13 subjects who were 'collected effectiveness evaluations beyond 3 months after the index BOTOX injection'.

During the surveillance period, 14 AEs occurred in 11 out of 667 subjects in the safety analysis set, showing an AE incidence proportion of 1.65%.

When analyzing AEs by SOC, most common AEs included 'Application site disorders' and 'Central & peripheral nervous system disorders' in 0.45% each (3/667 subjects), followed by 'Body as a whole - general disorders', 'Platelet, bleeding & clotting disorders', and 'Skin and appendages disorders' in 0.30% each (2/667 subjects), and 'Gastro-intestinal system disorders' and 'Urinary system disorders' in 0.15% each (1/667 subjects).

In the detailed analysis of reported AEs, 'EYELID PTOSIS', 'INJECTION SITE PAIN' and 'BRUISE' occurred in 0.30 % each (2/667 subjects, 2 cases each), 'MEDICINE INEFFECTIVE', 'TUBERCULOSIS', 'BURNING SENSATION', 'INJECTION SITE SWELLING', 'NAIL DISORDER', 'RASH ERYTHEMATOUS', 'CONSTIPATION', and 'RENAL FAILURE ACUTE' occurred in 0.15% each (1/667 subjects, 1 case each). Among these, 2 cases from 2 subjects (0.30%) were ADRs for which causal relationship to the study drug could not be excluded. The reported ADRs included 'INJECTION SITE PAIN' under "Application site disorders" in 0.30%.

During the surveillance period, 1 SAE was reported in 1 out of 667 subjects (0.15%) in the safety analysis set. 1 SAE was 'RENAL FAILURE ACUTE' under "Urinary system disorders". There were no serious ADRs for which causal relationship to the study drug could not be excluded.

During the surveillance period, 4 unexpected AEs were reported in 3 out of 667 subjects (0.45%) in the safety analysis set. In the detailed analysis of unexpected AEs, 'TUBERCULOSIS' ' under "Body as a whole - general disorders", 'BURNING SENSATION' under "Central & peripheral nervous system disorders", 'NAIL DISORDER' under "Skin and appendages disorders", and 'RENAL FAILURE ACUTE' under "Urinary system disorders" occurred in 0.15% each (1/667 subjects, 1 case). Among these, there were no ADRs for which causal relationship to the study drug could not be excluded.

During the surveillance period, 1 unexpected SAE was reported in 1 out of 667 subjects (0.15%) in the safety analysis set. One unexpected SAE was 'RENAL FAILURE ACUTE' under "Urinary system disorders". There were no unexpected serious ADRs for which causal relationship to the study drug could not be excluded.

When classifying the severity of the AEs into 3 categories of 'Mild', 'Moderate', and 'Severe', there were 12 'Mild' cases, 1 'Moderate' case, and 1 'Severe' case.
When classifying the outcomes of AEs into 4 categories of 'Ongoing', 'Resolved without

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sequelae adverse event', 'Resolved with sequelae adverse event', and 'Death', there were 3 cases of 'Ongoing' and 11 cases of 'Resolved without sequelae adverse event'.

When classifying the causal relationships of AE incidences to the study drug into 6 categories of 'Certain', 'Probable/likely', 'Possible', 'Unlikely', 'Conditional/unclassified', and 'Nonassessable/unclassifiable', there were 12 cases of 'Unlikely', 2 cases of 'Possible'.

When classifying the causal relationships of AE incidences to the injection procedure of the study drug into 6 categories of 'Certain', 'Probable/likely', 'Possible', 'Unlikely', 'Conditional/unclassified', and 'Nonassessable/unclassifiable', there were 12 cases of 'Unlikely', 2 cases of 'Possible'.

When classifying the presences of treatment after AE incidence into 2 categories of 'Yes' and 'No', There were 3 cases of 'Yes' and 11 cases of 'No'.

The result of investigators' overall evaluation of changes in lateral canthal lines for 376 subjects in the effectiveness analysis set showed that 99.73% (375/376 subjects) of the subjects was evaluated as 'Improved' and 0.27% (1/376 subjects) of the subjects was 'Unchanged'. In the effectiveness evaluation criteria, 'Improved' was considered as "Effectiveness" and 'Unchanged' and 'Worsened' were considered as "Ineffectiveness". The study drug was found to be 'effective' in 99.73% (375/376 subjects) and 'ineffective' in 0.27% (1/376 subjects).

In conclusion, the post marketing surveillance on Botox® Inj. 50 units showed no specific trend comparing to previously reported AE incidences and no specific factors that may affect the safety and effectiveness. Therefore, it is considered that administration of Botox® Inj. 50 units is safe and effective, and the use of Botox® Inj. 50 units will be continuously monitored in spontaneous reports or other studies.

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Ⅶ. Delivery Performance

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7. Delivery Performance

• Period: 04 Feb 2014 ~ 03 Feb 2018

(Unit: vial)

Period	Delivery Performance
1-1st (03 Feb 2014 ~ 03 Aug 2014)	44,287 (sample 246 vials included)
1-2nd (04 Aug 2014 ~ 03 Feb 2015)	42,726 (sample 68 vials included)
2-1st (04 Feb 2015 ~ 03 Aug 2015)	36,393 (sample 10,437 vials included)
2-2nd(04 Aug 2015 ~ 03 Feb 2016)	29,813 (sample 6,537 vials included)
3rd (04 Feb 2016 ~ 03 Feb 2017)	55,066 (sample 9,334 vials included)
4th (04 Feb 2017 ~ 03 Feb 2018)	60,830 (sample 2,769 vials included)
Total	269,115

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Ⅷ. Overseas Incidence of Adverse Events

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8. Overseas Incidence of Adverse Events

8.1 Periodic Safety Update Report in PBRER(01 Jan 2013 to 31 Dec 2013)

This is the twenty-second Periodic Safety Update Report (PSUR) for BOTOX® and BOTOX® COSMETIC (botulinum toxin type A) purified neurotoxin complex (US adopted name is onabotulinumtoxinA), and the second in Periodic Benefit-Risk Evaluation Report (PBRER) format as described in the International Conference on Harmonization (ICH) E2C(R2) Guideline (EMA/CHMP/ICH/544553/1998). This report summarizes safety information received by Allergan from worldwide sources between 01-January-2013 and 31-December-2013.

BOTOX® was first approved on 29-December-1989 in the United States (US). BOTOX® and BOTOX® COSMETIC are currently licensed worldwide for the treatment of a variety of disorders. However, not all indications are licensed in all countries. Licensed indications in the US, European Union (EU) member states, Canada and/or Australia (as per the Company Core Data Sheet [CCDS] version 16.1) include blepharospasm, including benign essential blepharospasm or cranial nerve VII disorders, and hemifacial spasm; strabismus; cervical dystonia (spasmodic torticollis); upper and lower limb spasticity associated with pediatric cerebral palsy; upper limb spasticity associated with stroke; spasmodic dysphonia; primary focal axillary hyperhidrosis; urinary incontinence due to neurogenic detrusor overactivity (NDO), e.g., spinal cord injury (SCI) or multiple sclerosis (MS); overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and frequency; prophylaxis of chronic migraine; and upper facial rhytides including forehead, lateral canthus, and glabellar lines.

The Reference Safety Information is the CCDS version 16.1 (August-2013). During the current reporting period, changes were made to CCDS in effect at the start of the period (version 15.0, September-2011). These changes included the addition of information for the newly-approved indication of overactive bladder (OAB), an update of data for the lateral canthus lines (crow's feet lines [CFL]) indication, revised wording for geriatric use, and addition of the event of 'dysphonia' as a post-marketing adverse drug reaction (ADR).

BOTOX® is classified within the pharmacotherapeutic group "Muscle relaxant, peripherally acting agent". The active ingredient in the Allergan-branded BOTOX® products is the same formulation of onabotulinumtoxinA. Botulinum toxin blocks cholinergic neurotransmission by preventing the release of acetylcholine and this mechanism of action is responsible for its activity in focal muscle relaxation. Additionally, BOTOX® may have a mechanistically similar but separate antinociceptive effect from its well-known effect on the neuromuscular junction.

The clinical effects of BOTOX® are largely dependent upon the anatomical site of injection. [redacted]

For the majority of indications, the route of administration is intramuscular. For the indications of NDO and OAB, the route is intradetrusor. For the indication of axillary hyperhidrosis, the route is intradermal. The dose of each individual injection varies as described in the prescribing information and may be adjusted according to the medical judgment of the prescribing medical professional. Globally, across all approved doses in all markets, the recommended dose for an indication ranges in general from 1.25 U to 400 U. The maximum cumulative dose in a 3-month interval should generally not exceed 400 U in adults. The maximum dose in pediatric patients (i.e., < 18 years old) in a 3-month interval should not exceed 8 U/kg, up to a maximum dose of

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300 U, whichever is lower. . Prescribers are also warned that the recommended dosages of BOTOX® are not interchangeable with other preparations of botulinum toxin.

In the current 1-year reporting period, a total of 4,138,275 vials of BOTOX® and 2,003,889 vials of BOTOX® COSMETIC were distributed globally, with an estimated worldwide patient exposure of 1,292,188 to 1,872,639 patient-years for BOTOX® and 2,386,698 patient-years for BOTOX® COSMETIC. Between product launch and the data lock point (DLP) of this report (31-December-2013) approximately 33,471,553 vials of BOTOX® and 13,651,675 vials of BOTOX® COSMETIC (a total of 47,123,228 vials) have been distributed worldwide, and cumulative post-marketing patient exposure is estimated at 31,183,521 to 35,461,541 patientyears. Cumulatively, an estimated 17,400 subjects have been treated globally with BOTOX® / BOTOX® Cosmetic in 123 Allergan-sponsored clinical trials up to 31-December-2013.

Based on reviews and evaluation of safety and efficacy data received in the current reporting period, the overall benefit-risk profiles of BOTOX® and BOTOX® COSMETIC remain favorable. Two signals, Joint subluxation and Guillain-Barré syndrome, were evaluated in the current reporting period and will remain ongoing signals for the next PSUR. New efficacy information received for the cosmetic treatment of CFL and glabellar lines supports the positive benefit-risk ratio for cosmetic indications.

Based on the safety information reviewed in the current reporting period, no update to the CCDS is warranted at this time.

In light of the worldwide experience, Allergan recommends that the arrangements for the prescribing and marketing of BOTOX® and BOTOX® COSMETIC be allowed to continue. Allergan continues to evaluate and monitor the safety profiles of BOTOX® and BOTOX® COSMETIC through routine and enhanced pharmacovigilance activities, and important identified and potential risks continue to be managed as specified in the EU-RMP version 7.1.

8.2 Periodic Safety Update Report in PBRER(01 Jan 2014 to 31 Dec 2014)

This is the twenty-third Periodic Safety Update Report (PSUR) for BOTOX® and BOTOX® Cosmetic (botulinum toxin type A) purified neurotoxin complex (US adopted name is onabotulinumtoxinA), and the third in Periodic Benefit-Risk Evaluation Report (PBRER) format as described in the International Conference on Harmonization (ICH) E2C(R2) Guideline (EMA/CHMP/ICH/544553/1998). This report summarizes safety information received by Allergan from worldwide sources between 01-January-2014 and 31-December-2014.

BOTOX was first approved on 29-December-1989 in the United States (US). BOTOX and BOTOX Cosmetic are currently licensed worldwide for the treatment of a variety of disorders. However, not all indications are licensed in all countries. Licensed indications in the US, European Union (EU), Canada and/or Australia (as per the Company Core Data Sheet [CCDS] version 17.0) include blepharospasm, including benign essential blepharospasm or cranial nerve VII disorders, and hemifacial spasm; strabismus; cervical dystonia (spasmodic torticollis); upper and lower limb spasticity associated with pediatric cerebral palsy; upper limb and lower limb (ankle) spasticity associated with stroke; spasmodic dysphonia; primary focal axillary hyperhidrosis; urinary incontinence due to neurogenic detrusor overactivity (NDO), e.g., spinal cord injury (SCI) or multiple sclerosis (MS); overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and frequency; prophylaxis of chronic migraine; and upper facial rhytides including forehead, lateral canthus, and glabellar lines.

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The Reference Safety Information is the CCDS version 17.0 (July-2014). During the current reporting period, changes were made to the CCDS that was in effect at the start of the period (version 16.1, August-2013). These changes included the addition of information for the newlyapproved indication of lower limb (ankle) spasticity associated with stroke in adults, the addition of lagophthalmos as a post-marketing adverse drug reaction (ADR) for cosmetic indications (i.e., glabellar lines and crow's feet lines), and updated information regarding neutralizing antibodies to botulinum toxin in patients treated for NDO.

BOTOX is classified within the pharmacotherapeutic group "Muscle relaxant, peripherally acting agent". The active ingredient in all Allergan-branded BOTOX products is the same formulation of onabotulinumtoxinA. Botulinum toxin blocks cholinergic neurotransmission by preventing the release of acetylcholine and this mechanism of action is responsible for its activity in focal muscle relaxation. Additionally, BOTOX may have a mechanistically similar but separate antinociceptive effect from its well-known effect on the neuromuscular junction. The clinical effects of BOTOX are largely dependent upon the anatomical site of injection.



For the majority of indications, the route of administration is intramuscular. For the indications of NDO and OAB, the route is intradetrusor. For the indication of axillary hyperhidrosis, the route is intradermal. The dose of each individual injection varies as described in the prescribing information and may be adjusted according to the medical judgment of the prescribing medical professional. Globally, across all approved doses in all markets, the recommended dose for an indication ranges in general from 1.25 U to 400 U. The maximum cumulative dose in a 3-month interval should generally not exceed 400 U in adults. The maximum dose in pediatric patients (i.e., < 18 years old) in a 3-month interval should not exceed 8 U/kg, up to a maximum dose of 300 U, whichever is lower. Prescribers are also warned that the recommended dosages of BOTOX are not interchangeable with other preparations of botulinum toxin.

Cumulatively, an estimated 17,400 subjects globally have been treated with BOTOX / BOTOX Cosmetic in 123 Allergan-sponsored clinical trials through 31-December-2013.

Cumulatively, between first product launch and 31-December-2014, approximately 53,916,220 vials of BOTOX / BOTOX COSMETIC have been distributed worldwide, resulting in an estimated worldwide exposure of 35 to 40 million patient-years.

Based on reviews and evaluation of safety and efficacy data received in the current reporting period, the overall benefit-risk profiles of BOTOX and BOTOX COSMETIC remain favorable.

Six signals were evaluated in the current reporting period, and the following five were closed:

- Potential risks characterized as important: Guillain-Barré syndrome (GBS) and Falls in post-stroke patients with focal spasticity of the ankle.
- Potential risk not characterized as important: Influenza / Influenza-like illness.
- Identified risk not characterized as important: Lagophthalmos (cosmetic indications involving treatment of glabellar lines and crow's feet lines).
- Refuted signal: Herpes infection.

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The signal Joint subluxation will remain an ongoing signal for presentation in the next PSUR.

New efficacy information received for the treatment of lower limb spasticity following stroke in adult patients supports the positive benefit-risk ratio for therapeutic spasticity indications.

On the basis of data reviewed for the current reporting period, no further changes are recommended to the CCDS.

In light of the worldwide experience, Allergan recommends that the arrangements for the prescribing and marketing of BOTOX and BOTOX COSMETIC be allowed to continue.

Allergan continues to evaluate and monitor the safety profile of BOTOX and BOTOX COSMETIC through routine and enhanced pharmacovigilance activities, and important identified and potential risks continue to be managed as specified in the EU-RMP version 7.4.

8.3 Periodic Safety Update Report in PBRER(01 Jan 2015 to 31 Dec 2015)

This is a Periodic Safety Update Report (PSUR) for BOTOX® and BOTOX® COSMETIC (botulinum toxin type A) purified neurotoxin complex (United States [US] adopted name is onabotulinumtoxinA) in Periodic Benefit-Risk Evaluation Report (PBRER) format as described in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2C(R2) Guideline (EMA/CHMP/ICH/544553/1998). This report is written for submission in countries that require a 1-year PSUR and summarizes safety information received by Allergan from worldwide sources between 01-January-2015 and 31-December-2015.

This report contains all required safety data for Allergan's onabotulinumtoxinA-branded products, which are BOTOX, BOTOX COSMETIC, VISTABEL®, VISTABEX®, and BOTOX Vista 50, and it also includes reports on botulinum toxin type A in which the manufacturer is not identified. Reference to BOTOX COSMETIC in this report will include the use of other internationally licensed cosmetic brand names such as VISTABEL, VISTABEX, and BOTOX Vista 50. Within this report, data for BOTOX are presented separately from those for BOTOX COSMETIC (whenever possible).

BOTOX was first approved on 29-December-1989 in the US. BOTOX and BOTOX COSMETIC are currently licensed worldwide for the treatment of a variety of disorders. However, not all indications are licensed in all countries. Licensed indications in the US, European Union (EU), Canada and/or Australia (as per the company core data sheet [CCDS] version 17.0) include blepharospasm, including benign essential blepharospasm or cranial nerve VII disorders, and hemifacial spasm; strabismus; cervical dystonia (spasmodic torticollis); upper and lower limb spasticity associated with pediatric cerebral palsy (in the EU lower limb spasticity only); upper limb and lower limb (ankle) spasticity associated with stroke; spasmodic dysphonia; primary focal axillary hyperhidrosis; urinary incontinence due to neurogenic detrusor overactivity (NDO); overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and frequency; prophylaxis of chronic migraine; and upper facial rhytides including forehead, lateral canthus, and glabellar lines (GL).

BOTOX is classified within the pharmacotherapeutic group "Muscle relaxant, peripherally acting agent". The active ingredient in all Allergan-branded BOTOX products is the same formulation of botulinum toxin type A. Botulinum toxin blocks cholinergic neurotransmission by preventing

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the release of acetylcholine and this mechanism of action is responsible for its activity in focal muscle relaxation. Additionally, BOTOX may have a mechanistically similar but separate antinociceptive effect from its well-known effect on the neuromuscular junction. The clinical effects of BOTOX are largely dependent upon the anatomical site of injection.

[redacted]

For the majority of indications, the route of administration is intramuscular. For the indications of NDO and OAB, the route is intradetrusor. For the indication of axillary hyperhidrosis, the route is intradermal. The dose of each individual injection varies as described in the prescribing information and may be adjusted according to the medical judgment of the prescribing medical professional. Globally, across all approved doses in all markets, the recommended dose for an indication ranges in general from 1.25 U to 400 U. The maximum cumulative dose in a 3-month interval should generally not exceed 400 U in adults. The maximum dose in pediatric patients (i.e., < 18 years old) in a 3-month interval should not exceed 8 U/kg or 300 U, whichever is lower. Prescribers are also warned that the recommended dosages of BOTOX are not interchangeable with other preparations of botulinum toxin.

Cumulatively, an estimated 14,898 subjects have been treated globally with BOTOX/BOTOX COSMETIC in more than 123 Allergan-sponsored clinical trials up to the data lock point (DLP) of 31-December-2015.

Cumulatively, between first product launch and 31-December-2015, approximately 43,066,371 vials of BOTOX and 18,285,187 vials of BOTOX COSMETIC (61,351,558 vials combined) were distributed globally. Patient-year exposure for BOTOX and BOTOX COSMETIC combined was 39,733,522 to 45,320,698 patient-years (13,670,452 to 19,257,627 patient-years for BOTOX and 26,063,071 patient-years for BOTOX COSMETIC).

Based on reviews and evaluation of safety and efficacy data received in the current reporting period, the overall benefit-risk profiles of BOTOX and BOTOX COSMETIC remain favorable.

One signal (Joint subluxation) was evaluated in the current reporting period; the signal was closed and refuted.

New efficacy information received for the cosmetic treatment of lateral canthus lines (crow's feet lines) and GL supports the positive benefit-risk ratio for cosmetic indications. New efficacy information received for the treatment of urinary incontinence due to NDO, the treatment of overactive bladder, and chronic migraine prophylaxis supports the positive benefit-risk ratio for these indications.

The reference safety information is the CCDS version 17.0 (July-2014), which was in effect throughout the reporting period. During the current reporting period, no changes were made to CCDS. On the basis of data reviewed for the current reporting period, no further changes are recommended to the CCDS.

In light of the worldwide experience, Allergan recommends that the arrangements for the prescribing and marketing of BOTOX and BOTOX COSMETIC be allowed to continue.
Allergan continues to evaluate and monitor the safety profile of BOTOX and BOTOX

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COSMETIC through routine and enhanced pharmacovigilance activities.

8.4 Periodic Safety Update Report in PBRER(01 Jan 2016 to 31 Dec 2016)

This is a Periodic Safety Update Report (PSUR) for BOTOX® and BOTOX® COSMETIC (botulinum toxin type A) purified neurotoxin complex (United States [US] adopted name is onabotulinumtoxinA) in Periodic Benefit-Risk Evaluation Report (PBRER) format as described in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2C(R2) Guideline (EMA/CHMP/ICH/544553/1998). This report is written for submission in countries that require a one-year PSUR and summarizes safety information received by Allergan from worldwide sources between 01-January-2016 and 31-December-2016.

This report contains all required safety data for Allergan's onabotulinumtoxinA-branded products, which are BOTOX, BOTOX COSMETIC, VISTABEL®, VISTABEX®, and BOTOX Vista 50, and it also includes reports on botulinum toxin type A in which the manufacturer is not identified. Reference to BOTOX COSMETIC in this report will include the use of other internationally licensed cosmetic brand names such as VISTABEL, VISTABEX, and BOTOX Vista 50. Within this report, data for BOTOX are presented separately from those for BOTOX COSMETIC (whenever possible).

BOTOX was first approved on 29-December-1989 in the US. BOTOX and BOTOX COSMETIC are currently licensed worldwide for the treatment of a variety of disorders. However, not all indications are licensed in all countries. Licensed indications in the US, European Union (EU), Canada and/or Australia (as per the company core data sheet [CCDS] version 17.0) include blepharospasm, including benign essential blepharospasm or cranial nerve VII disorders, and hemifacial spasm; strabismus; cervical dystonia (spasmodic torticollis); upper and lower limb spasticity associated with pediatric cerebral palsy; upper limb and lower limb (ankle) spasticity associated with stroke; spasmodic dysphonia; primary focal axillary hyperhidrosis; urinary incontinence due to neurogenic detrusor overactivity (NDO); overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and frequency; prophylaxis of chronic migraine; and upper facial rhytides including forehead lines (FHL), lateral canthus lines (crow's feet lines [CFL]), and glabellar lines (GL).

BOTOX is classified within the pharmacotherapeutic group "Muscle relaxant, peripherally acting agent". The active ingredient in all Allergan-branded BOTOX products is the same formulation of botulinum toxin type A. Botulinum toxin blocks cholinergic neurotransmission by preventing the release of acetylcholine and this mechanism of action is responsible for its activity in focal muscle relaxation. Additionally, BOTOX may have a mechanistically similar but separate antinociceptive effect from its well-known effect on the neuromuscular junction. The clinical effects of BOTOX are largely dependent upon the anatomical site of injection.



For the majority of indications, the route of administration is intramuscular. For the indications of NDO and OAB, the route is intradetrusor. For the indication of axillary hyperhidrosis, the route is intradermal. The dose of each individual injection varies as described in the prescribing

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information and may be adjusted according to the medical judgment of the prescribing medical professional. Globally, across all approved doses in all markets, the recommended dose for an indication ranges in general from 1.25 U to 400 U. The maximum cumulative dose in a 3-month interval should generally not exceed 400 U in adults. The maximum dose in pediatric patients (i.e., < 18 years old) in a 3-month interval should not exceed 8 U/kg or 300 U, whichever is lower. Prescribers are also warned that the recommended dosages of BOTOX are not interchangeable with other preparations of botulinum toxin.

Cumulatively, an estimated 14,978 subjects have been treated globally with BOTOX/BOTOX COSMETIC in more than 123 Allergan-sponsored clinical trials up to the data lock point (DLP) of 31-December-2016.

Cumulatively, between first product launch and 31-December-2016, approximately 47,813,660 vials of BOTOX and 20,631,516 vials of BOTOX COSMETIC (68,445,176 vials combined) were distributed globally. Estimated patient-year exposure for BOTOX and BOTOX COSMETIC combined was 43,619,887 to 49,947,821 patient-years (14,881,259 to 21,209,191 patient-years for BOTOX and 28,738,629 patient-years for BOTOX COSMETIC).

Based on the review and evaluation of safety and efficacy data received in the current reporting period, the overall benefit-risk profiles of BOTOX and BOTOX COSMETIC remain favorable. The reference safety information for the reporting period covered by this PSUR was based upon the CCDS version 17.0 (July-2014), which was in effect at the start of the period. Changes were made to the CCDS during the reporting period of this PSUR, and CCDS version 18.0 was approved in February-2016.

Four signals were identified during the current reporting period. Severe cutaneous adverse reactions and mediastinitis with off-label esophageal indications were closed and refuted and brow ptosis was closed as an identified risk not categorized as important. Joint subluxation was closed as a signal in PSUR 24 (01-January-2015 to 31-December-2015) but was reinstated as a signal in the current PSUR period as requested in the Assessment Report for PSUR 24, and is kept ongoing. On the basis of data reviewed for the current reporting period, no additional changes to the BOTOX/BOTOX COSMETIC CCDS are required.

New efficacy information received for the cosmetic treatment of upper facial rhytides supports the positive benefit-risk ratio for cosmetic indications. New efficacy information received for chronic migraine prophylaxis and the treatment of lower/upper limb spasticity supports the positive benefit-risk ratio for these indications.

In light of the worldwide experience, Allergan recommends that the arrangements for the prescribing and marketing of BOTOX and BOTOX COSMETIC be allowed to continue. Allergan continues to evaluate and monitor the safety profile of BOTOX and BOTOX COSMETIC through routine and enhanced pharmacovigilance activities.

8.5 Periodic Safety Update Report in PBRER(01 Jan 2017 to 31 Dec 2017)

This is a Periodic Safety Update Report (PSUR) for BOTOX® and BOTOX® COSMETIC (botulinum toxin type A) purified neurotoxin complex (United States [US] and Canada adopted name is onabotulinumtoxinA) in Periodic Benefit-Risk Evaluation Report (PBRER) format as described in the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E2C(R2) Guideline

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(EMA/CHMP/ICH/544553/1998). This report is written for submission in countries that require a one-year PSUR and it summarizes safety information received by Allergan from worldwide sources between 01-January-2017 and 31-December-2017.

This report contains all required safety data for Allergan's onabotulinumtoxinA-branded products, which are BOTOX, BOTOX COSMETIC, VISTABEL®, VISTABEX®, and BOTOX Vista 50, and it also includes reports on botulinum toxin type A in which the manufacturer is not identified. Reference to BOTOX COSMETIC in this report will include the use of other internationally licensed cosmetic brand names such as VISTABEL, VISTABEX, and BOTOX Vista 50. Within this report, data for BOTOX are presented separately from those for BOTOX COSMETIC (whenever possible).

BOTOX was first approved on 29-December-1989 in the US. BOTOX and BOTOX COSMETIC are currently licensed worldwide for the treatment of a variety of disorders. However, not all indications are licensed in all countries. Licensed indications in the US, European Union (EU), Canada and/or Australia (as per the Company Core Data Sheet [CCDS] version 19.0) include blepharospasm, including benign essential blepharospasm or cranial nerve VII disorders, and hemifacial spasm; strabismus; cervical dystonia (spasmodic torticollis); upper and lower limb spasticity associated with pediatric cerebral palsy; upper limb and lower limb spasticity associated with stroke; spasmodic dysphonia; primary focal axillary hyperhidrosis; urinary incontinence due to neurogenic detrusor overactivity (NDO); overactive bladder (OAB) with symptoms of urinary incontinence, urgency, and frequency; prophylaxis of chronic migraine; and upper facial rhytides including forehead lines (FHL), lateral canthus lines (LCL), or crow's feet lines [CFL]), and glabellar lines (GL).

BOTOX is classified within the pharmacotherapeutic group "Muscle relaxant, peripherally acting agent". The active ingredient in all Allergan-branded BOTOX products is the same formulation of botulinum toxin type A. Botulinum toxin blocks cholinergic neurotransmission by preventing the release of acetylcholine and this mechanism of action is responsible for its activity in focal muscle relaxation. Additionally, BOTOX may have a mechanistically similar but separate antinociceptive effect from its well-known effect on the neuromuscular junction (NMJ). The clinical effects of BOTOX are largely dependent upon the anatomical site of injection.



For the majority of indications, the route of administration is intramuscular. For the indications of NDO and OAB, the route is intradetrusor. For the indication of axillary hyperhidrosis, the route is intradermal. The dose of each individual injection varies as described in the prescribing information and may be adjusted according to the medical judgment of the prescribing medical professional. Globally, across all approved doses in all markets, the recommended dose for an indication ranges in general from 1.25 U to 400 U. The maximum cumulative dose in a 3-month interval should generally not exceed 400 U in adults. The maximum dose in pediatric patients (i.e., < 18 years old) in a 3-month interval should not exceed 8 U/kg or 300 U, whichever is lower. Prescribers are also warned that the recommended dosages of BOTOX are not

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interchangeable with other preparations of botulinum toxin.

Cumulatively, an estimated 15,330 subjects have been treated globally with BOTOX/BOTOX COSMETIC in more than 123 Allergan-sponsored clinical trials up to the data lock point (DLP) of 31-December-2017.

Cumulatively, between first product launch and 31-December-2017, approximately 56,655,744 vials of BOTOX and 24,039,704 vials of BOTOX COSMETIC (80,695,448 vials combined) were distributed globally. Estimated worldwide cumulative patient-year exposure for BOTOX and BOTOX COSMETIC combined was 49,380,238 to 56,877,238 patient-years (17,064,718 to 24,561,717 patient-years for BOTOX and 32,315,521 patient-years for BOTOX COSMETIC).

In the current 1-year PSUR reporting period, approximately 7,301,391 vials of BOTOX and 3,015,593 vials of BOTOX COSMETIC (10,316,984 vials combined) were distributed globally. Estimated worldwide patient-year exposure for BOTOX and BOTOX COSMETIC combined from 01-January-2017 to 31-December-2017 was 5,760,351 to 6,929,420 patient-years (2,183,459 to 3,352,528 patient-years for BOTOX and 3,576,892 patient-years for BOTOX COSMETIC).

There were no actions taken regarding BOTOX/BOTOX COSMETIC for safety reasons by either a health authority or by the sponsor during the current reporting period.

Based on the review and evaluation of safety and efficacy data received in the current reporting period, the overall benefit-risk profiles of BOTOX and BOTOX COSMETIC remain favorable.

The reference safety information (RSI) in effect at the start of the reporting period was the CCDS version 18.0 (February-2016). The following signals were identified and evaluated during the current reporting period. Joint subluxation was an ongoing signal at the start of the reporting period, and it will remain ongoing. The new signals Dry eye and Muscle twitching/involuntary muscle contractions were closed as identified risks not categorized as important, and Xerophthalmia was closed as refuted. Based on these analyses, dry eye and localized muscle twitching/involuntary muscle contractions were added to the CCDS version 19.0 dated June-2017 (the RSI for this PSUR) as adverse drug reactions (ADRs) from post-marketing experience for BOTOX and BOTOX COSMETIC. No further safety changes to the CCDS are recommended based on the data reviewed for the current PSUR reporting period.

New efficacy information received from the Allergan clinical development program for chronic migraine prophylaxis in adolescents does not suggest efficacy of BOTOX for this indication in this population. New efficacy information received for major depressive disorder in adult females may support a positive benefit-risk ratio for this indication. New efficacy information received from GSK Japan for the authorized indication of spasmodic dysphonia demonstrates the efficacy of BOTOX for the treatment of adductor spasmodic dysphonia.

In light of the worldwide experience, Allergan recommends that the arrangements for the prescribing and marketing of BOTOX and BOTOX COSMETIC be allowed to continue. Allergan continues to evaluate and monitor the safety profiles of BOTOX and BOTOX COSMETIC through routine pharmacovigilance activities.

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8.6 Safety summary (01 Jan 2018 to 03 Feb 2018)

1. Introduction

This is a safety summary for BOTOX® (botulinum toxin type A purified neurotoxin complex). It summarizes safety information received by Allergan from worldwide sources between 01-January-2018 and 03-February-2018 and was prepared for the health authority of Korea. In accordance with Volume 9A guidelines, medically confirmed reports from the following sources are included in this summary: spontaneous notifications from Healthcare Professionals; serious, treatment-related events reported in clinical study (including sponsored, unsponsored, observational studies, and post authorization surveillance); literature reports; and reports received from Regulatory Authorities. Non-medically confirmed reports from the same sources are also included in the summary though presented in separate Line Listings.

2. Safety Summary

BOTOX

This report includes a total of 352 adverse event reports for which a total of 773 adverse events were received; of these, 66 events were serious and included 50 unlisted events. A total of 273 adverse event reports were medically confirmed and 79 were non-medically confirmed. There were 2 cases involving a fatal outcome (Section 3).

BOTOX COSMETIC

This report includes a total of 364 adverse event reports for which a total of 639 adverse events were received; of these, one event was serious and unlisted. A total of 310 adverse event reports were medically confirmed and 54 were non-medically confirmed. There were no cases involving a fatal outcome.

3. Presentation of Fatal Cases

BOTOX

The following fatal cases were received during the reporting period for BOTOX:

Table 2 Fatal Cases

MCN	Serious Event(s)	MAH comment
[redacted]	Death	A [redacted] patient died of an unknown cause 9 days following the second BOTOX injection for muscle spasms. Dose regimen was 240 units, single, intramuscular to unspecified areas. The patient had first received BOTOX 240 units injected to upper limbs due to severe spasms in left upper limb about 3 months earlier. No problem was found after the second administration of BOTOX and the patient returned home. Nine days following the second BOTOX injection, he was found dead. The cause of death and the further details regarding the event were unknown. There is insufficient

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MCN	Serious Event(s)	MAH comment
		information provided at this time for a proper case assessment.
[redacted]	Dyspnoea	A [redacted] patient died from difficulty breathing following BOTOX injection in both sides of the front neck (off-label use) for an unknown indication. After BOTOX injection, the patient went home from the clinic and ended up in the Emergency Room with difficulty breathing. The patient died on an unknown date and the cause of death was difficulty breathing. Per Warnings and Precautions in product information, care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX injected directly into salivary glands, the oro-lingualpharyngeal region, esophagus and stomach.

BOTOX COSMETIC

There were no cases involving a fatal outcome for BOTOX COSMETIC.

4. Frequency of Reported Events

4.1 Events by System Organ Class (SOC)

BOTOX

The majority of events were reported in the General disorders and administration site conditions SOC (34%, 262/773, 221 listed, 41 unlisted). The most frequently reported adverse events (≥ 1%) were Drug ineffective (135), Injection site pain (17), Drug ineffective for unapproved indication (12), Asthenia (9), and Therapeutic response decreased (8).

A total of 178 events were reported in the Injury, poisoning and procedural complications SOC (23%, 178/773, 0 listed, 178 unlisted). The most frequently reported adverse events (≥ 1%) were: Off label use (124), Product preparation error (11), and Wrong technique in product usage process (8).

A total of 77 events were reported in the Nervous system disorders SOC (10%, 77/773, 22 listed, 55 unlisted). The most frequently reported adverse events (≥ 1%) were: Headache (11) and Dizziness (8).

Of the remaining SOCs, 5 preferred terms comprised ≥ 1% (≥ 8 events) of the total events reported: Dysphagia (13) in the Gastrointestinal disorders SOC, Eyelid ptosis (12) in the Eye disorders SOC, Dyspnoea (10) in the Respiratory, thoracic and mediastinal disorders SOC, Muscular weakness (10) in the Musculoskeletal and connective tissue disorders SOC, and Influenza (8) in the Infections and infestations SOC.

No cases with distant spread of toxin were reported.

A tabulation of all adverse events by SOC and listedness is presented in 01-Main PSUR Report Events by SOC from All Cases.

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BOTOX COSMETIC

The majority of events were reported in the General disorders and administration site conditions SOC (51%, 326/639, 308 listed, 18 unlisted). The most frequently reported adverse events (≥ 1%) were Drug ineffective (233), Therapeutic response decreased (28), Injection site pain (9), and Injection site swelling (7). No other adverse events in the General disorders and administration site conditions SOC were reported at a frequency of ≥ 1%.

A total of 156 events were reported in the Injury, poisoning and procedural complications SOC (24%, 156/639, 5 listed, 151 unlisted). The most frequently reported adverse events (≥ 1%) were: Off label use (75), Product preparation error (24), Poor quality drug administered (20), Wrong technique in product usage process (13), and Product storage error (8).

A total of 36 events were reported in the Nervous system disorders SOC (4.7%, 36/773, 13 listed, 23 unlisted). The most frequently reported adverse event (≥ 1%) was Headache (8). No other adverse events in the Nervous system disorders SOC were reported at a frequency of ≥ 1%.

Of the remaining SOCs, only one preferred term comprised ≥ 1% (≥ 7 events) of the total events reported: Eyelid ptosis (12) in the Eye disorders SOC.

No cases with distant spread of toxin were reported.

A tabulation of all adverse events by SOC and listedness is presented in 01-Main PSUR Report Events by SOC from All Cases.

4.2 Routine Safety Signal Review

During this reporting interval, there were no new safety signals revealed via routine signal detection activity for BOTOX and BOTOX COSMETIC and no changes to the overall risk-benefit profile of BOTOX and BOTOX COSMETIC.

5. Conclusion

Following the review of safety information received in the period between 01-January-2018 and 03-February-2018, no changes to the overall risk-benefit profile of BOTOX and BOTOX COSMETIC have been observed. Allergan will continue to evaluate and monitor the safety profile of BOTOX and BOTOX COSMETIC through routine pharmacovigilance activities.
In light of the above worldwide experience, Allergan finds that the risk-benefit profile for BOTOX and BOTOX COSMETIC has not changed, and recommends that the arrangement for the prescribing and marketing of BOTOX and BOTOX COSMETIC be allowed to continue.

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Ⅸ. Overseas Marketing and Authorization Status Data

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9. Overseas Marketing and Authorization Status Data (Periodic Safety Update Report in PBRER(01 Jan 2017 to 31 Dec 2017))

9.1 Marketed drug exposure

The worldwide sales distribution data for the current PSUR reporting period is provided in Table 5–18. A total of 7,301,391 vials of BOTOX and 3,015,593 vials of BOTOX COSMETIC were distributed globally from 01-January-2017 to 31-December-2017.

Table 5–18 **Worldwide Distribution of BOTOX and BOTOX COSMETIC Vials During the Period 01-January-2017 to 31-December-2017**

Region	BOTOX			BOTOX COSMETIC			Total Vials Distributed
	50 U vial	100 U vial	200 U vial	50 U vial	100 U vial	200 U vial	
EU-28	177,863	1,140,492	107,153	489,312	0	0	1,914,820
US	0	1,671,715	536,972	558,506	1,621,223	0	4,388,416
ROW	514,196	3,046,554	106,446	207,939	59,174	79,439	4,013,748
Worldwide[a]	**692,059**	**5,858,761**	**750,571**	**1,255,757**	**1,680,397**	**79,439**	**10,316,984**

[a] Worldwide totals include European Union (EU)-28, United States (US), and Rest of World (ROW).

Patient exposure estimates for the current reporting period are presented as patient-years in Table 5-19.

Table 5-19 **Summary of Patient Exposure by Region During the Period 01-January-2017 to 31-December-2017**

Region	Patient Exposure (patient-years)		
	BOTOX	BOTOX COSMETIC	Total
EU-28	932,381	850,257	1,782,638
US	586,549	2,510,040	3,096,589
ROW	664,529-1,833,598	216,595	881,124-2,050,193
Worldwide	**2,183,459-3,352,528**	**3,576,892**	**5,760,351- 6,929,420**

The cumulative worldwide sales distribution data are provided in Table 5–21. A total of 56,655,744 vials of BOTOX and 24,039,704 vials of BOTOX COSMETIC (a combined total of 80,695,448 vials) were distributed globally in the period of 01-January-1990 to 31-December-2017.

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Table 5–21 **Worldwide Distribution of BOTOX and BOTOX COSMETIC Vials During the Period 01-January-1990 to 31-December-2017**

Region	BOTOX			BOTOX COSMETIC			Total vials distributed
	50 U vial	100 U vial	200 U vial	50 U vial	100 U vial	200 U vial	
EU-28	758,353	12,339,339	432,527	4,145,418	55,974	0	17,731,611
US	0	17,873,828	1,894,462	3,141,091	14,128,123	0	37,037,504
ROW	2,712,353	20,336,994	307,888	887,748	1,223,500	457,850	25,926,333
Worldwide[a]	**3,470,706**	**50,550,161**	**2,634,877**	**8,174,257**	**15,407,597**	**457,850**	**80,695,448**

[a] Worldwide totals include European Union (EU)-28, United States (US), and Rest of World (ROW).

Estimated patient exposure in each region during the cumulative period, expressed in patient-years, is provided in Table 5–22. Patient-year exposure for BOTOX and BOTOX COSMETIC combined was 49,380,238 to 56,877,238 patient-years (17,064,718 to 24,561,717 patient-years for BOTOX and 32,315,521 patient-years for BOTOX COSMETIC).

Table 5–22 **Summary of Patient Exposure by Region During the Period 01-January-1990 to 31-December-2017**

Region	Patient exposure (patient-years)		
	BOTOX	BOTOX COSMETIC	Total
EU-28	8,061,002	7,350,986	15,411,988
US	5,131,737	23,381,453	28,513,190
ROW	3,871,978-11,368,978	1,583,082	5,455,060-12,952,062
Worldwide	**17,064,718-24,561,717**	**32,315,521**	**49,380,238-56,877,238**

9.2 Overseas Authorization Status

BOTOX received first regulatory approval on 29-December-1989 in the US. BOTOX and BOTOX COSMETIC are currently licensed worldwide for the treatment of a variety of disorders. However, not all indications are licensed in all countries.

In the European region, the cosmetic product is approved under the trade name VISTABEL or VISTABEX. In Japan, the cosmetic product is approved under the trade name BOTOX Vista 50.

Details of the currentmarketing authorization status of BOTOX and BOTOX COSMETIC, including information on cumulative approval dates, approved indications, local trade names, and registered vial sizes are presented in this report [Appendix 6].

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X. Approved Label Comparison Table

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10. Approved Label Comparison Table

Category	Korea (Revised:)	US (Revised Feb/2016)
Effectiveness	1. 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 or older. 2. BOTOX® is indicated in the treatment of dynamic equinus foot deformity by spasticity in two years of age or older patients with cerebral palsy. 3. BOTOX® is indicated for the treatment of sign and symptom of cervical dystonia. 4. BOTOX® is indicated for the treatment continuous severe primary axillary hyperhidrosis that is inadequately managed topical agents and interferes with daily activities in 18 years of age or older adults. 5. Muscle spasticity: BOTOX® is indicated in the management of upper limb spasticity associated with stroke in adults 18 years of age or older. 6. BOTOX® is indicated for the temporary improvement in the appearance of the following upper facial lines in adults ≥18, ≤75 years of age: ● moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity ● moderate to severe lateral canthal lines (crow's feet lines) associated with orbicularis oculi activity ● moderate to severe crow's feet lines and glabellar lines, when treated simultaneously	**1 INDICATIONS AND USAGE** **1.1 Glabellar Lines** BOTOX Cosmetic (onabotulinumtoxinA) for injection is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients. **1.2 Lateral Canthal Lines** BOTOX Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients.
Usage· Dosage	1) Strabismus BOTOX® is intended for injection into extra ocular muscles utilizing the electrical Activity recorded from the tip of the injection needle as a guide to placement within the target muscle.	**2 DOSAGE AND ADMINISTRATION** **2.1 Instructions for Use** The potency Units of BOTOX Cosmetic (onabotulinumtoxinA) for injection are specific to

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Category	Korea (Revised:)	US (Revised Feb/2016)
	Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic techniques. An injection of BOTOX® is prepared by drawing into a sterile 1.0mL tuberculin syringe an amount of the properly reconstituted toxin (see Dilution Table) slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needles, preferably a 1 ½" 27 gauge). Injection volume in excess of the intended dose is expelled through the needle into an appropriate waste container to assure patency of the needle and to confirm that there is no syringe-needle leakage. A new, sterile, needle and syringe should be used to enter the vial on each occasion for dilution or removal of BOTOX®. It is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection. *Note:* The recommended volume of BOTOX® injected for treatment of strabismus is 0.05 mL to 0.15 mL per muscle. Method: The initial listed doses of the reconstituted BOTOX® (see Dilution Table below) typically create paralysis of injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2 to 6 weeks and gradually resolves over a similar time period. Over-corrections 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 (hereafter U). 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 U to 2.5 U in any one muscle. B. For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 U to 5.0 U in any one muscle. C. For persistent VI nerve palsy of one month or longer duration: 1.25 U to 2.5	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 Cosmetic cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [see Description (11)]. Indication specific dosage and administration recommendations should be followed. In treating adult patients for one or more indications with BOTOX and BOTOX Cosmetic, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval. The safe and effective use of BOTOX Cosmetic depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. Physicians administering BOTOX Cosmetic must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease, especially when injecting near the lungs. **2.2 Preparation and Dilution Technique** BOTOX Cosmetic is supplied in single-use 50 Units and 100 Units per vial. Prior to intramuscular injection, reconstitute each vacuum-dried vial of BOTOX Cosmetic with sterile, preservative-free 0.9% Sodium Chloride Injection USP. Draw up the proper amount of diluent in the appropriate size needle and syringe to obtain a reconstituted solution at a concentration of 4 Units/0.1 mL and a total treatment dose of 20 Units in 0.5 mL for glabellar lines and 24 Units in 0.6 mL for lateral canthal lines (see Table 1). Then slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX Cosmetic with the saline by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX Cosmetic should be administered within 24 hours after reconstitution. During this time period, reconstituted BOTOX Cosmetic should be stored in a refrigerator (2° to 8°C). BOTOX Cosmetic vials are for single-use only. Discard any remaining solution. **Table 1: Dilution Instructions for BOTOX Cosmetic Vials (100 Units and 50 Units)**

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<table>
<tr><th>Category</th><th>Korea (Revised:)</th><th>US (Revised Feb/2016)</th></tr>
<tr>
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<td>U 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 U.

2) Blepharospasm

For blepharospasm, reconstituted BOTOX® (see Dilution Table) is injected using a sterile, 27 - 30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 - 2.5 U (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. 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 5.0 U 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, but it is rare to have the effect be permanent.

The cumulative dose of BOTOX® treatment in a 30-day period should not exceed 200 U.</td>
<td>
<table>
<tr><th>Diluent* Added to 100 Unit Vial</th><th>Resulting Dose Units per 0.1 mL</th><th>Diluent* Added to 50 Unit Vial</th><th>Resulting Dose Units per 0.1 mL</th></tr>
<tr><td>2.5 mL</td><td>4Units</td><td>1.25 mL</td><td>4Units</td></tr>
</table>
* Preservative-free 0.9% Sodium Chloride Injection, USP Only

Reconstituted BOTOX Cosmetic 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. Do not freeze reconstituted BOTOX Cosmetic.

2.3 Administration
Draw at least 0.5 mL (for glabellar lines) or 0.6 mL (for lateral canthal lines) of the properly reconstituted toxin into the sterile syringe, preferably a tuberculin syringe and expel any air bubbles in the syringe barrel. Remove the needle used to reconstitute the product and attach a 30-33 gauge needle. Confirm the patency of the needle.

Glabellar Lines

Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. This creates a frown or “furrowed brow”. The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles. An effective dose for facial lines is determined by gross observation of the patient’s ability to activate the superficial muscles injected.

In order to reduce the complication of ptosis the following steps should be taken:

• Avoid injection near the levator palpebrae superioris, particularly in patients with</td>
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<table>
<tr><th>Category</th><th>Korea (Revised:)</th><th>US (Revised Feb/2016)</th></tr>
<tr><td></td><td>
3) Pediatric cerebral palsy

Reconstituted BOTOX® (see Dilution Table) is injected using a sterile, 23 - 26 gauge needle. It is administered as a divided dose through single injections into the medial and lateral heads of the affected gastrocnemius muscle.

In hemiplegia, the initial recommended total dose is 4 U/kg body weight in the affected limb.

In diplegia, the initial recommended total dose is 6 U/kg body weight divided between the affected limbs.

Clinical improvement generally begins within the first two weeks after injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes but not more frequently than every three months.

4) Cervical Dystonia

Reconstituted BOTOX® (see Dilution Table) is injected using an appropriately sized needle (usually 25, 27, 30 gauge). The following doses are recommended for individual type.

<table>
<tr><th>Cervical Dystonia Classification</th><th>Muscle Groupings</th><th>Total Dosage ; Number of Sites</th></tr>
<tr><td>Type 1
Head rotated toward side of shoulder elevation</td><td>Sternocleidomastoid
Levator scapulae
Scalene
Splenius capitis
Trapezius</td><td>50-100 U: at least 2 sites
50 U: 1-2 sites
25-50 U: 1-2 sites
25-75 U: 1-3 sites
25-100 U: 1-8 sites</td></tr>
<tr><td>Type II
Head rotation only</td><td>Sternocleidomastoid</td><td>25-100 U: at least 2 sites if >25 U given</td></tr>
<tr><td>Type III</td><td>Sternocleidomastoid</td><td>25-100 U at posterior border: at</td></tr>
</table>
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larger brow depressor complexes.

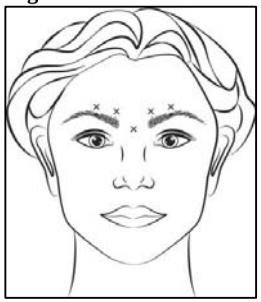
• Lateral corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

• Ensure the injected volume/dose is accurate and where feasible kept to a minimum.

• Do not inject toxin closer than 1 cm above the central eyebrow.

Inject 4 Units/0.1 mL of reconstituted BOTOX Cosmetic intramuscularly into each of 5 sites, 2 in each corrugator muscle and 1 in the procerus muscle for a total dose of 20 Units (see Figure 1). Typically the initial doses of reconstituted BOTOX Cosmetic induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week.

The duration of effect of BOTOX Cosmetic for glabellar lines is approximately 3-4 months. The safety and effectiveness of dosing with BOTOX Cosmetic more frequently than every 3 months have not been clinically evaluated.

Figure 1:

</td></tr>
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Category	Korea (Revised:)	US (Revised Feb/2016)

<table>
<tr>
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<td>
<table>
<tr><td>Head tilted toward side of shoulder elevation</td><td>Levator scapulae
Scalene
Trapezius</td><td>least 2 sites if >25 U given
25-100 U: at least 2 sites
25-75 U: at least 2 sites
25-100 U: 1-8 sites</td></tr>
<tr><td>Type IV
Bilateral posterior cervical muscle spasm with elevation of the face</td><td>Splenius capitis and cervicis</td><td>50-200 U: 2-8 sites, treat bilaterally (This is the total dose and not the dose for each side of the neck)</td></tr>
</table>

For cervical dystonia, localization of the involved muscles with electromyographic guidance may be useful. In case of difficulty in distinguishing the individual muscle, inject with electromyography. No more than 50 U should be given at any more injection site. In case of inject into the sternocleidomastoid, do not excess 100 U. The sternocleidomastoid muscle should not be injected bilaterally as there is an increased risk of occurring of dysphagia. The maximum total dose is not usually more than 200 U and the repeated dose will be adjusted according the response to the initial injection. One dose should not be excess 300 U. Diluted BOTOX® should be injected for not excess 0.25 ml per injection site. For considering appropriate injection volume, concentration of diluted BOTOX® is 5 U/0.1ml and 10 U/0.1ml.

Clinical improvement generally occurs within the first two weeks after injection. The maximum clinical benefit generally occurs approximately six weeks post-injection. Repeat doses should be administered when the clinical effect of a previous injection diminishes. Injection duration is recommended as more than 10 weeks. Generally, the duration of therapeutic effect reported in the clinical trials showed substantial variation (from 2 to 33 weeks), with a typical duration of approximately 12 weeks, depending on the patient's individual disease and response. Dosing must tailored to the individual patient.
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Lateral Canthal Lines

Lateral canthal lines arise largely from the activity of the orbicularis oculi muscles around the eye responsible for blinking and eyelid closure. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet lines) which originate from the lateral canthus. The distribution of these radial lines differs among patients.

Injections should be given with the needle bevel tip up and oriented away from the eye. Inject 4 Units/0.1 mL of reconstituted BOTOX Cosmetic into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side). The first injection (A) should be approximately 1.5-2.0 cm temporal to the lateral canthus and just temporal to the orbital rim. If the lines in the lateral canthal region are above and below the lateral canthus, inject per Figure 2. Alternatively, if the lines in the lateral canthal region are primarily below the lateral canthus, inject per Figure 3.

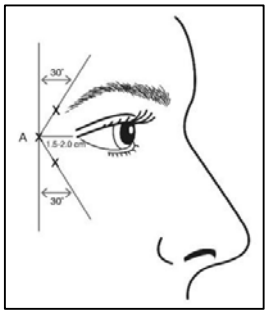
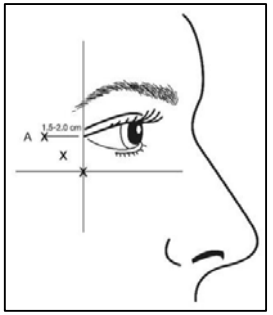
Figure 2


Figure 3


For simultaneous treatment with glabellar lines, the dose is 24 Units for lateral canthal lines and 20 Units for glabellar lines (see Glabellar Lines Administration and Figure 1), with a total dose of 44 Units.

The safety and effectiveness of dosing with BOTOX Cosmetic more frequently than every
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<table>
<tr><th>Category</th><th>Korea (Revised:)</th><th>US (Revised Feb/2016)</th></tr>
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5) Primary axillary hyperhidrosis

BOTOX® is reconstituted with 0.9% non-preserved sterile saline (100 U/4 mL). Using a 30 gauge needle, 50 U of BOTOX® (2 mL) is injected intradermally to each axilla approximately 1-2 cm apart. The hyperhidrotic area may be defined by using standard staining techniques, e.g. Minor's iodine-starch test. 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. Doses other than 50 U per axilla have not been studied and therefore cannot be recommended.

Clinical improvement generally occurs within the first week after injection. The median duration of response is 7.5 months in the patients injected 50 U per axilla. Repeat injection of BOTOX® can be administered when the clinical effect of a previous injection diminished and the treating physician deems it necessary. Injections should not be repeated more frequently than every 16 weeks.

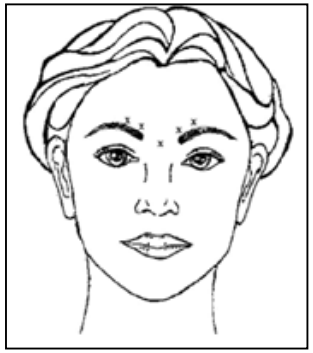
6) Upper limb spasticity

The exact dosage and number of injection sites should be tailored to the individual based on the size, number and location of muscles involved, the severity of spasticity, presence of local muscle weakness, and the patient response to previous treatment. Clinical improvement in muscle tone is seen four to six weeks following treatment.

Table. BOTOX Dosing by Muscle for Upper Limb Spasticity
<table>
<tr><td>Muscle</td><td>Total dosage</td><td>: Number of sites</td></tr>
<tr><td>Biceps brachii</td><td>100-200U</td><td>: up to 4 sites</td></tr>
<tr><td>Flexor digitorum profundus</td><td>15-50 U</td><td>: 1-2 sites</td></tr>
<tr><td>Flexor digitorum sublimis</td><td>15-50 U</td><td>: 1-2 sites</td></tr>
<tr><td>Flexor carpi radialis</td><td>15-60 U</td><td>: 1-2 sites</td></tr>
<tr><td>Biceps brachii</td><td>10-50 U</td><td>: 1-2 sites</td></tr>
</table>
</td><td>
3 months have not been clinically evaluated.

3 DOSAGE FORMS AND STRENGTHS
For injection: 50 Units, vacuum-dried powder in a single-use vial for reconstitution
For injection: 100 Units, vacuum-dried powder in a single-use vial for reconstitution
</td></tr>
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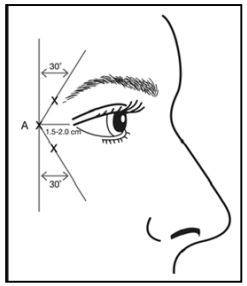
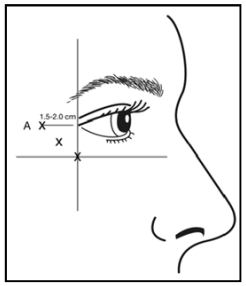
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	In the clinical trial, doses are not over 360 U, injected into individual muscle. In clinical studies, patients were re-injected at 12 to 16 week following treatment. The degree of muscle spasticity at the time of reinjection may necessitate alterations in the dose of BOTOX® and muscles to be injected. Reconstituted BOTOX® is injected using a sterile 25-30 gauge needle for superficial muscles, and a longer needle(22 gauge) for deeper musculature. Localization of the involved muscles with electromyographic guidance or nerve stimulation techniques may be useful. 7) Glabellar lines It is reconstituted with 0.9% non-preserved sterile saline to make 50 U/1.25 mL (4 U/0.1 mL). Using a 30-33 gauge needle, 0.1 mL is administrated to 2 injections in each corrugator muscle and 1 injection in procerus muscle for total dose of 20 U/0.5 mL (see Figure below). In order to reduce the risk of ptosis, injections near the levator palpebrae superioris muscle must be avoid.  Injections in the corrugator muscle must be done in the central part of that muscle, at least	

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	1 cm above the arch of the eyebrows. Care should be taken to ensure that BOTOX® is not injected into a blood vessel when it is injected. Before injection, the thumb or index finger are to be placed firmly below the orbital rim in order to prevent extravasation below the orbital rim. The needle should be oriented superiorly and medially during the injection. The injection volume should be accurate. Glabellar facial lines arise from the activity of the corrugator and orbicularis oculi muscles. These muscles move the brow medially, and the procerus and depressor supercilii pull the brow inferiorly. This creates a frown or "furrowed brow". The location, size, and use of the muscles vary markedly among individuals. Lines induced by facial expression occur perpendicular to the direction of action of contracting facial muscles. An effective dose for facial lines is determined by gross observation of the patient's ability to activate the superficial muscles injected. The duration of activity of the product for glabellar lines is approximately 3-4 months. The safety and effectiveness of more frequent dosing with the product has not been clinically evaluated and is not recommended. Typically the initial doses of reconstituted the product induce chemical denervation of the injected muscles one to two days after injection, increasing in intensity during the first week. 8) Lateral Canthal Lines (Crow's Feet Lines) Lateral canthal lines arise largely from the activity of the orbicularis oculi muscles around the eye responsible for blinking and eyelid closure. Forceful contraction of the orbicularis oculi results in lateral and radially oriented folds (crow's feet lines) which originate from the lateral canthus. The distribution of these radial lines differs among patients. Injections should be given with the needle bevel tip up and oriented away from the eye. Using a 30-33 gauge needle, inject 4 Units/0.1 mL of reconstituted BOTOX® into 3 sites per side (6 total injection points) in the lateral orbicularis oculi muscle for a total of 24 Units/0.6 mL (12 Units per side). The first injection (A) should be approximately 1.5-2.0 cm temporal	

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	to the lateral canthus and just temporal to the orbital rim. If the lines in the lateral canthal region are above and below the lateral canthus, inject per Figure 1. Alternatively, if the lines in the lateral canthal region are primarily below the lateral canthus, inject per Figure 2. Figure 1 Figure 2   For simultaneous treatment with glabellar lines, the dose is 24 Units for crow's feet lines and 20 Units for glabellar lines (see Glabellar Lines Administration and the corresponding Figure), with a total dose of 44 Units. The safety and effectiveness of dosing with BOTOX® more frequently than every 3 months have not been clinically evaluated. 9) Common items - Dilution method To reconstitute vacuum-dried BOTOX® injection, use sterile normal saline without a preservatives; 0.9% Sodium Chloride Injection is the recommended diluent. Draw up the proper amount of diluent in the appropriate size syringe (see Dilution table below). Since the product is denatured by bubbling or similar violent agitation, inject the diluent into the vial gently. Discard the vial if a vacuum does not pull the diluent into the vial. Record the date and time	

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<tr><td></td><td>
of reconstitution on the space on the label. BOTOX® should be administered within 24 hours after reconstitution.

During this time period, reconstituted the product should be stored in a refrigerator (2° to 8°C). Reconstituted the product 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.

< Dilution Table >
<table>
<tr><th>Diluent Added
(0.9% Sodium Chloride)</th><th>Resulting Dose U
(Unit/0.1 mL)</th></tr>
<tr><td>0.5 mL</td><td>10.0 U</td></tr>
<tr><td>1.0 mL</td><td>5.0 U</td></tr>
<tr><td>1.25 mL</td><td>4.0 U</td></tr>
<tr><td>2.0 mL</td><td>2.5 U</td></tr>
<tr><td>4.0 mL</td><td>1.25 U</td></tr>
</table>
Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the product 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).

10) Instructions for Safe Use

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 U, 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
</td><td></td></tr>
</table>

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Category	Korea (Revised:)	US (Revised Feb/2016)
	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), ptosis, or when excessive weakness or atrophy is present in the target muscle(s).	
Precautions for Use	1. Warnings The active ingredient of this drug is botulinum toxin type A, produced from Hall strain botulinum. Thus, physicians administering this drug must be fully aware of the precautions in the use of this drug, and follow strictly the administration method and dosage guideline. Physicians administering this drug should also fully understand the relevant neuromuscular and orbital anatomy, anatomy of the area involved, any alteration due to prior surgical procedures, and standard electromyographic techniques. The recommended dosage and frequency of administration for this drug should not be exceeded. A. Distant spread of toxin effect Botulinum toxin may spread beyond the site of local injection, producing symptoms consistent with botulinum toxin effects. The symptoms including acute muscle weakness, loss of strength, dysphonia, dysphasia, dysarthria, urinary incontinence, breathing difficulties, dysphagia, diplopia, and ptosis may occur. Swallowing and breathing difficulties can be life-threatening and there have been reports of death resulting from the spread of toxin effect. Children treated for spastic cerebral palsy is particularly at high risk. However, these symptoms can also occur in adults treated for spastic cerebral palsy or other conditions. Cases of symptoms described above have been reported at doses comparable to those used to treat cervical dystonia and at lower doses. B. Hypersensitivity Serious or immediate hypersensitivity reactions have been rarely reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema and dyspnea. One case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently	**5 WARNINGS AND PRECAUTIONS** **5.1 Lack of Interchangeability between Botulinum Toxin Products** **The potency Units of 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 Cosmetic 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 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, 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 an underlying condition 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 and upper limb spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory

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	the causal agent was not reliably determined. If such a reaction occurs after administration of this drug, the drug should be discontinued and an appropriate measure should be taken. C. Pre-existing neuromuscular disorders Patients with peripheral motor neuropathic disease (e.g., amyotrophic lateral sclerosis, motor neuropathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) may be at increased risk of significant systemic reactions including severe dysphagia and respiratory compromise from typical doses of this drug. According to clinical reference, severe hypersensitive reaction has been rarely reported in patients with known or unknown neuromuscular disease when treated with typical doses of botulinum toxin. Some of these patients experienced persistent dysphagia lasting for several months, and required use of a feeding tube. D. Dysphagia and breathing difficulties Treatment with BOTOX® and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting 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 oropharyngeal muscles that control swallowing or breathing. 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 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 difficulities, including respiratory	disorders occur. 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), 24 Units (for lateral canthal lines), 44 Units (for simultaneous treatment of lateral canthal lines and 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), strabismus, or chronic migraine at the labeled doses have been reported. **5.3 Serious Adverse Reactions with Unapproved Use** Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established. **5.4 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 Cosmetic 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.

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	failure. Patients treated with botulinum toxin may require immediate medical attentions should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin. E. There have been few 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 BOTOX® is unknown. F. During the administration of this drug for the treatment of strabismus, retrobulbar hemorrhage may occur from needle penetration into the orbit, which may compromise retinal circulation. It is recommended the use of appropriate instruments to decompress the orbit which can be easily influenced be accessible. In addition, ocular penetrations by needles have been also reported. An ophthalmoscope to diagnose this condition should be used. Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double-vision, past-pointing. Covering the affected eye may alleviate these symptoms. G. Blepharospasm When this drug is administered especially in patients with VII nerve disorder, reduced blinking may occur, which can lead to corneal exposure, persistent epithelial defect and corneal ulceration. There was one case of corneal perforation in an aphakic eye due to this effect, which required corneal grafting. For patients with prior surgery history, a careful testing of corneal sensation in the applicable eyes should be employed, and avoidance of injection into the lower lid can reduce the risk of ectropion. Vigorous treatment of any epithelial defect should be employed. The treatments for such case include protective eye drops, ointment, therapeutic soft contact lens, or closure of the eye by patching or other means.	**5.5 Cardiovascular System** There have been reports following administration of BOTOX of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. Use caution when administering to patients with pre-existing cardiovascular disease. **5.6 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 when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from onabotulinumtoxinA *[see Warnings and Precautions (5.7)]*. **5.7 Dysphagia and Breathing Difficulties** Treatment with BOTOX and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with preexisting 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 oropharyngeal muscles that control swallowing or breathing.*[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 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

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	H. Lack of interchangeability The toxin contents may vary by each botulinum toxin product, therefore, unit of one botulinum toxin product cannot be converted into unit of any other botulinum toxin product. I. Injection in or near vulnerable anatomic structures Care should be taken when injecting in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX® injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. Pneumothorax associated with injection procedure has been reported following the administration of BOTOX® near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices. J. Pulmonary Effects of BOTOX® in Adult Patients with Compromised Respiratory Status Treated for Upper Limb Spasticity In some patients with compromised respiratory status treated with BOTOX® for upper limb spasticity, reduced lung function (i.e., decrease in Forced Vital Capacity [FVC] of ≥15%) was reported. Upper respiratory tract infections were also reported more frequently compared to placebo (See Section K). K. Bronchitis and Upper Respiratory Tract Infections in Adult Patients Treated for Upper Limb Spasticity Bronchitis was reported more frequently in patients treated for upper limb spasticity with BOTOX®, compared to placebo. In patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently in	respiratory failure. Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia 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)]*. **5.8 Pre-existing Conditions at the Injection Site** Caution should be used when BOTOX Cosmetic treatment is used in the presence of inflammation at the proposed injection site(s), ptosis, or when excessive weakness or atrophy is present in the targeted muscle(s). **5.9 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm** Reduced blinking from BOTOX Cosmetic 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. **5.10 Spatial Disorientation, Double Vision or Past-pointing in Patients Treated for Strabismus** Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past pointing. Covering the affected eye may alleviate these symptoms. **5.11** Human Albumin and Transmission of Viral Diseases

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	patients treated with BOTOX® compared to placebo. L. There have been rare spontaneous reports of death sometimes associated with aspiration pneumonia in children with severe cerebral palsy after treatment with botulinum toxin. Caution should be exercised when treating pediatric patients who have significant neurologic debility, dysphagia, or have a recent history of aspiration pneumonia or lung disease. M. Serious Adverse Reactions with Unapproved Use Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established. 2. The product should not be administered to the following patients. A. Patients with known hypersensitivity to any ingredients of the product. B. Patients with systemic neuromuscular junctional disorders (myasthenia gravis Lambert-Eaton syndrome, amyotrophic lateral sclerosis, etc.) – the disease may be worsen due to muscle relaxant activity of the product. C. Patients with severe respiratory disorders who require the treatment of cervical dystonia. D. Women who are pregnant or might be pregnant, and are breast-feeding. E. Patients with the presence of infection at the proposed injection site(s). 3. The product should be administered with caution to the following patients.	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 Cosmetic (onabotulinumtoxinA) for injection are discussed in greater detail in other Spread of Toxin Effects *[see Warnings and Precautions (5.2)]* Hypersensitivity [see Contraindications (4.1) and Warnings and Precautions (5.4)] Dysphagia and Breathing Difficulties [see Warnings and Precautions (5.7)] **6.1 Clinical Trials Experience** Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, but have different labeled Indications and Usage. Therefore, adverse events observed with the use of BOTOX also have the potential to be observed with the use of BOTOX Cosmetic. In general, adverse reactions occur within the first week following injection of BOTOX Cosmetic 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)]*.

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<td>
A. Patients receiving muscle relaxant (tubocurarine chloride, dantrolene sodium, etc.) - there is a risk of increased muscle relaxation or dysphagia.
B. Patients receiving muscle relaxing activity including spectinomycin hydrochloride, aminoglycoside antibiotics (gentamicin sulfate, neomycin sulfate), polypeptide antibiotics (polymyxin sulfate B), tetracycline antibiotics, lincosamide antibiotics, muscle relaxant (baclofen, etc.), anticholinergics (hyoscine butylbromide, trihexyphenidyl HCI, etc.), benzodiazepines and benzodiazepine-like compounds (diazepam, etizolam, etc.), benzamides (tiapride HCI, sulpiride, etc.) - there is a risk of increase of muscle relaxation or dysphagia.

4. Adverse Events
A. General information

There have been reports the followings the treatment with botulinum toxin, including sometimes dysphagia, pneumonia and/or significant debility, or rarely deaths associated with anaphylaxis.

In addition, there have been also reports of adverse events involving cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. The exact relationship of these adverse events to botulinum toxin has not been established.

The following adverse events have been reported since this drug has been marketed, and the causal relationship to botulinum toxin was ‘unknown’: skin rash (including erythema multiforme, urticaria, psoriasiform eruption), pruritus, and allergic reaction.

In general, adverse reactions occur within the first week following injection of the drug, and while generally transient may have duration of several months.

A localized pain, infection, inflammation, paresthesia, hypoesthesia, tenderness, bruising, and tightening, swelling, erythema, bleeding, and burning sensation at the injection site, and hypertonia at the injection site and adjacent muscles, which are associated with the injection may occur. Symptoms associated with flu-like symptoms (e.g., nausea, fever, myalgia) have been reported after treatment. Needle-related pain and/or anxiety may result in vasovagal responses (i.e hypotension and syncope) which may require appropriate medical therapy.
</td>
<td>
Glabellar Lines
Table 2 lists selected adverse reactions reported by >1% of BOTOX Cosmetic treated subjects (N=405) aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of BOTOX Cosmetic in the improvement of the appearance of glabellar lines.

Table 2: Adverse Reactions Reported by >1% of the BOTOX Cosmetic treated Patients and More Frequent than in Placebo-treated Patients in Double-blind, Placebo-controlled Clinical Studies of Treatment of Glabellar Lines
<table>
<tr><th>Adverse Reactions by System Organ Class</th><th>BOTOX Cosmetic (N=405)</th><th>Placebo (N=130)</th></tr>
<tr><td>General Disorders and Administration Site Conditions
Facial pain</td><td>6 (1%)</td><td>0 (0%)</td></tr>
<tr><td>Nervous System Disorders
Facial paresis</td><td>5 (1%)</td><td>0 (0%)</td></tr>
<tr><td>Eye Disorders
Eyelid ptosis</td><td>13 (3%)</td><td>0 (0%)</td></tr>
<tr><td>Musculoskeletal and Connective Tissue Disorder
Muscular weakness</td><td>6 (1%)</td><td>0 (0%)</td></tr>
</table>
Lateral Canthal Lines
Table 3 lists selected adverse reactions reported within 90 days following injection by >1% of BOTOX Cosmetic treated subjects (N=526) aged 18 to 75 who were evaluated in two randomized, double-blind, placebo-controlled clinical studies to assess the use of BOTOX Cosmetic in the improvement of the appearance of lateral canthal lines alone.

Table 3: Adverse Reaction Reported by ≥1% of BOTOX Cosmetic treated Patients and More Frequent than in Placebo-treated Patients Within 90 Days, in Double-blind, Placebo-controlled Clinical Studies of Treatment of Lateral Canthal Lines
</td>
</tr>
</table>

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<table>
<tr><th>Category</th><th>Korea (Revised:)</th><th>US (Revised Feb/2016)</th></tr>
<tr><td></td><td>Localized muscle weakness at the injected area represents the expected pharmacological action of botulinum toxin. However, weakness of adjacent muscles may result from the spread of toxin. Patients with blepharospasm or cervical dystonia may develop weakness of muscles distant from the injected area or an increased electrophysiological jitter (jitter, temporary waveform instability) unrelated to electrophysiological abnormality following administration of this drug.

B. Strabismus

Extraocular muscle adjacent to the injection site can be affected, causing ptosis or vertical deviation, especially with high doses of the drug. The incidence rates of adverse reactions in 2,058 adults who received a total of 3,650 injections for horizontal strabismus are as follow:

Ptosis: 15.7%

Vertical deviation: 16.9%

Inducing paralysis in one or more extraocular muscles may produce spatial disorientation, double vision or past-pointing. Covering the affected eye may alleviate these symptoms.

The incidence rate of ptosis was 0.9% after inferior rectus injection and 37.7% after superior rectus injection. The incidence rates of adverse reactions reported to persist for 6 months in 3,104 patients who received a total of 5,587 injections of horizontal muscle are as follow:

Ptosis: 0.3%

Vertical deviation greater than two prism diopters: 2.1%

In these patients, nine cases of scleral perforations were caused by the injection procedure itself. A vitreous hemorrhage occurred in one case and later cleared. No retinal detachment or visual loss was reported in any case. 16 cases of retrobulbar hemorrhage occurred. Decompression of the orbit after five minutes was initiated to restore retinal circulation. No visual loss was reported due to retrobulbar hemorrhage. Papillary change consistent with</td><td>
<table>
<tr><th>Adverse Reactions by System Organ Class</th><th>BOTOX Cosmetic 24 units (N=526)</th><th>Placebo (N=530)</th></tr>
<tr><td>Eye Disorders
Eyelid edema</td><td>5 (1%)</td><td>0 (0%)</td></tr>
</table>

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity. Treatment with botulinum toxins may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin.

In three Lateral Canthal Line trials, 916 subjects (517 subjects at 24 Units and 399 subjects at 44 Units) treated with BOTOX Cosmetic had specimens analyzed for antibody formation. Among the 916 BOTOX Cosmetic treated subjects, 14 subjects (1.5%) developed binding antibodies and no subjects (0%) developed the presence of neutralizing antibodies.

The data reflect the subjects whose test results were considered positive or negative for neutralizing activity to BOTOX Cosmetic 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 antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BOTOX Cosmetic with the incidence of antibodies 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 botulinum toxin 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.

6.3 Post-Marketing Experience
Because these reactions are reported voluntarily from a population of uncertain size, it is</td></tr>
</table>

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Category	Korea (Revised:)	US (Revised Feb/2016)
	ciliary ganglion damage was observed in 5 eyes (Adie's pupil). There has been a case of anterior segment ischemia in a patient who received the injection of this drug in the medial rectus muscle for the treatment of esotropia. C. Blepharospasm The most frequently reported adverse reactions in a study conducted in patients with blepharospasm who received an average dose per eye of 33 U (injected at 3~5 sites) of this drug included ptosis (20.8%), superficial punctuate keratitis (6.3%), and eye-dryness (6.3%). These adverse reactions were mild or moderate except for one case of ptosis, which was rate severe. Other adverse reactions reported in prior studies include the following (in an order of incidence): irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following local injection. In two cases (one case of an aphakic eye) of patients with VII nerve disorder who received the injection of this drug in the orbicularis muscle, serious corneal exposure, persistent epithelial defect and corneal ulceration resulting from reduced blinking were reported. A patient with an aphakic eye had perforation, which required corneal grafting. One case of acute angle closure glaucoma was reported in a patient with blepharospasm one day after receiving an injection of botulinum toxin, however the patient recovered 4 months later after laser iridotomy and trabeculectomy. In addition, exacerbation of myasthenia gravis, focal facial paralysis, and syncope have been reported after treatment of blepharospasm. An appropriate therapy should be taken if anopia or conjunctivitis sometimes occurs. According to the domestic PMS study conducted for 6 years, 41 of a total of 660 patients (6.2%) experienced adverse reactions, and the common adverse reactions include 17 cases of ptosis (2.6%), 5 cases of local swelling (0.8%), 3 cases of epiphora (0.5%), 3 cases of eye	not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. 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 (5.4, 5.7)]*. 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. New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The following adverse reactions by System Organ Class have been identified during post-approval use of BOTOX/BOTOX Cosmetic: **Ear and labyrinth disorders** Hypoacusis; tinnitus; vertigo **Eye disorders** Diplopia; lagophthalmos; strabismus; visual disturbances; vision blurred **Gastrointestinal disorders** Abdominal pain; diarrhea; dry mouth; nausea; vomiting **General disorders and administration site conditions** Denervation; malaise; pyrexia **Metabolism and nutrition disorders** Anorexia **Musculoskeletal and connective tissue disorders** Muscle atrophy; myalgia **Nervous system disorders**

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Category	Korea (Revised:)	US (Revised Feb/2016)
	irritation (0.5%), 3 cases of lagophthalmos (0.5%), 3 cases of weakness of muscle (0.5%), and 3 cases of eye dryness (0.5%). Unknown adverse events include 2 cases of tightness at the injection site (0.3%), 2 cases of muscle hypertonia (0.3%), 2 cases of conjunctival congestion (0.3%) and one case of ophthalmodynia (0.2%). D. Cervical dystonia In double-blind, open-label studies conducted in patients with cervical dystonia to evaluate the safety, the most frequently reported adverse reactions after administration of this drug include dysphagia (19%), upper respiratory infection (12%), neck pain (11%) and headache (11%). Adverse reactions reported in 2~10% of patients in another study are presented below in an order of incidence rate: 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. The most common serious adverse reactions associated with the use of BOTOX® injection is dysphagia with about 20% of these cases also reporting dyspnea. Most of dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms. In addition, there have been reports of a case of a female patient who developed brachial plexopathy two days after injection of 120 U of BOTOX® for the treatment of cervical dystonia, and reports of patients who developed dysphonia. The most common adverse reactions in the treatment of spasmodic torticollis include the following: dysphagia, pain and irritation at the injection site, localized muscle weakness and symptomatic general weakness, malaise. However, malaise was reported also from patients who received placebo. Dysphagia, symptomatic general weakness and localized muscle weakness may be attributable to an extension of the pharmacology of this drug resulting from the spread of the toxin outside the injected muscles. Adverse reactions associated with the dosage of this drug are more common in female patients. Therefore, the dose should be	Brachial plexopathy; dysarthria; facial palsy; hypoaesthesia; localized numbness; myasthenia gravis; paresthesia; peripheral neuropathy; radiculopathy; syncope **Respiratory, thoracic and mediastinal disorders** Aspiration pneumonia; dyspnea; respiratory depression and/or respiratory failure **Skin and subcutaneous tissue disorders** Alopecia, including madarosis; hyperhidrosis; pruritus; skin rash (including erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption) **7 DRUG INTERACTIONS** No formal drug interaction studies have been conducted with BOTOX Cosmetic (onabotulinumtoxinA) for injection. **7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission** Co-administration of BOTOX Cosmetic 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. **7.2 Anticholinergic Drugs** Use of anticholinergic drugs after administration of BOTOX Cosmetic may potentiate systemic anticholinergic effects. **7.3 Other Botulinum Neurotoxin Products** 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. **7.4 Muscle Relaxants** Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX Cosmetic.

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<table>
<tr><th>Category</th><th>Korea (Revised:)</th><th>US (Revised Feb/2016)</th></tr>
<tr><td></td><td>appropriately adjusted according to the size of muscle. Other adverse reactions include nausea, drowsiness, headache, numbness, spasticity and contusion.

In a total of 68 cases of the domestic PMS cases, 3 cases (4.4%) of adverse reactions were reported, including 2 cases of myalgia (2.9%), an unknown adverse reaction, and one case of spasticity (1.5%).

E. Pediatric cerebral palsy

Safety of this drug was evaluated in patients with pediatric cerebral palsy for the treatment of dynamic equines foot deformity due to spasticity. As expected from other muscle injection procedure, a localized pain was reported in these patients following the injection. Adverse reactions associated with all of the treatments were mild to moderate in severity.

The most frequently reported treatment-emergent adverse reactions include falling, leg pain, localized muscle weakness, and asthenia. The percentage of patients who experienced any of these events at least once during the study is presented below.

<table><tr><td colspan="2">This drug, n = 215</td></tr><tr><td>falling</td><td>falling</td></tr><tr><td>Leg pain</td><td>Leg pain</td></tr><tr><td>Muscle weakness, localized</td><td>Muscle weakness, localized</td></tr><tr><td>asthenia</td><td>asthenia</td></tr></table>
Falling may occur due to ankle location and walking posture and/or localized muscle weakness. Localized muscle weakness may be attributable to anticipated pharmacology of botulinum toxin.

Other treatment-emergent adverse reactions reported in 1% of patients are: leg cramp, fever, knee pain, ankle pain at the injection site following treatment and drowsiness. The frequency of incidence of adverse reactions from clinical experiences are as follow (very frequent</td><td>8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects: Pregnancy Category C.

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

When BOTOX Cosmetic (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 5 times the average high human dose for glabellar lines and lateral canthal lines of 44 Units on a body weight basis (Units/kg).

When BOTOX Cosmetic 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 is approximately 1.4 times the average human dose based on Units/kg, and the developmental no-effect dose of 0.25 Units/kg in rabbits is less than the average high human dose based on Units/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 22 times the average high human dose based on Units/kg.

8.3 Nursing Mothers</td></tr>
</table>

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Category	Korea (Revised:)	US (Revised Feb/2016)
	(≥1/10); frequent (≥1/100, <1/10)) • Very frequent: viral infection, otitis • Frequent: myalgia, myasthenia, urinary incontinence, delirium, abnormal walking, malaise, erythema and numbness Of a total of 572 cases collected from the domestic PMS studies, 8 adverse events (1.4%) were reported, including 4 cases of pain at the injection site (0.7%), 3 cases of fever (0.5%), and one case of rash (0.2%). There was no unknown adverse reaction. F. Primary axillary hyperhidrosis Adverse reactions reported from clinical studies are categorized by body organ and the frequency of incidence: [frequent (≥1/100, <1/10), rare (≥1/1000, <1/100)]. Nervous system: headache (frequent); vascular system: flushing (frequent); gastrointestinal system: nausea (rare); skin and subcutaneous tissue: hyperhidrosis (non-axillary sweating) (frequent), pruritus (rare); musculoskeletal system and connective tissue: muscle weakness, myalgia, arthropathy, severe pain (rare); general and injection-site related symptoms: reaction and pain at the injection site (frequent), asthenia, injection site edema, pain at the injection site (rare). In the primary axillary sweating treatment, non-axillary sweating was reported in 4.5% of patients within one month following the injection, and no anatomical pattern of onset site was observed. Of these patients, 30% had their symptoms cleared within 4 months. Weakness of arm was rarely reported (0.7%), which was mild and transient, did not required a treatment and resolved without sequela. This adverse reaction is expected to be associated with the treatment or injection technique or both. In rare case, neurological examination can be considered for muscle weakness reported. In addition, to ensure the accurate subcutaneous injection, it is recommended to re-evaluate the injection technique prior to initiating the second injection.	It is not known whether BOTOX Cosmetic is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX Cosmetic is administered to a nursing woman. **8.4 Pediatric Use** Safety and effectiveness in patients below the age of 18 years have not been established. **8.5 Geriatric Use** *Glabellar Lines* In the two initial glabellar lines clinical studies of BOTOX Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older *[see Clinical Studies (14)]*. *Lateral Canthal Lines* In the two lateral canthal lines clinical studies of BOTOX Cosmetic, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older. **10 OVERDOSAGE** Excessive doses of BOTOX Cosmetic (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms. Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, these patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization. The person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection *[see Boxed Warning and Warnings and Precautions (5.2, 5.7)]*.

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Category	Korea (Revised:)	US (Revised Feb/2016)
	G. Upper Limb Spasticity The safety of BOTOX® was evaluated in 339 patients who received BOTOX® for the treatment of post-stroke upper limb spasticity. In general, most of adverse reactions reported were mild or moderate. Treatment-emergent adverse reactions reported in 1~4% of patients are presented in an order of frequency of incidence: arm pain and hypertonia. Fever and flu-like symptoms were also reported in approximately 1% of patients. Treatment-emergent adverse reactions reported in less than 1% of patients are presented in an order of frequency of incidence: hyperaphia, arthralgia, asthenia, bursitis, dermatitis, headache, hypersensitivity at the injection site, discomfort, nausea, paresthesia, orthostatic hypotension and pruritus. In 82 patients who received a single dose of BOTOX® for the treatment of post-stroke lower-limb spasticity, the safety was evaluated. The treatment-emergent adverse reactions reported are: injury resulting from an accident (1.2%), disequilibrium (1.2%), and paresthesia (1.2%). The reported adverse reactions were mild or moderate. Of 56 patients who received an injection of BOTOX® in a double-blind study, 44 received the second injection in an open-label study. Additional treatment-emergent adverse reactions reported are: hypertonia (4.5%), myasthenia (2.3%), headache (2.3%), and hyperkinesias (2.3%). H. Glabellar lines Table below lists selected adverse reactions reported by ≥1% of BOTOX® treated subjects (N=405) aged 18 to 75 who were evaluated in the randomized, placebo-controlled clinical studies to assess the use of BOTOX in the improvement of the appearance of glabellar lines.	If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care. 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. **16 HOW SUPPLIED/STORAGE AND HANDLING** **BOTOX Cosmetic** is supplied in a single-use vial in the following sizes: 50 Units: NDC 0023-3919-50 100 Units: NDC 0023-9232-01 The top and bottom flaps of the BOTOX Cosmetic cartons have a tamper-evident seal that contains a translucent silver Allergan logo. Vials of BOTOX Cosmetic 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.) Each BOTOX Cosmetic vial label and carton also contains the U.S. License number: 1145. 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 if:

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<table>
<tr><th>Category</th><th>Korea (Revised:)</th><th>US (Revised Feb/2016)</th></tr>
<tr><td></td><td>
Table: Adverse Reaction Reported by ≥1% of the BOTOX® treated Patients and More Frequent than in Placebo-treated Patients in Double-blind, Placebo-controlled Clinical Studies of Treatment of Glabellar Lines
<table>
<tr><th>Adverse Reactions by System Organ Class</th><th>BOTOX® group (N=405)</th><th>Placebo group (N=130)</th></tr>
<tr><td>General Disorders and Administration Site Conditions</td><td></td><td></td></tr>
<tr><td>Facial Pain</td><td>6 (1%)</td><td>0 (0%)</td></tr>
<tr><td>Nervous System Disorders</td><td></td><td></td></tr>
<tr><td>Facial paresis</td><td>5 (1%)</td><td>0 (0%)</td></tr>
<tr><td>Eye disorders</td><td></td><td></td></tr>
<tr><td>Eyelid ptosis</td><td>13 (3%)</td><td>0 (0%)</td></tr>
<tr><td>Musculoskeletal and Connective Tissue Disorders</td><td></td><td></td></tr>
<tr><td>Muscular weakness</td><td>6 (1%)</td><td>0 (0%)</td></tr>
</table>
I. Crow’s Feet Lines

Below table lists selected adverse reactions reported within 90 days following injection by ≥1% of BOTOX® treated subjects (N=526) aged 18 to 75 who were evaluated in two randomized, double-blind, placebo-controlled clinical studies to assess the use of BOTOX® in the improvement of the appearance of crow’s feet lines alone.

Table: Adverse Reaction Reported by ≥1% of BOTOX® treated Patients and More Frequent than in Placebo treated Patients Within 90 Days, in Double-blind, Placebo-controlled Clinical Studies of Treatment of Crow’s Feet Lines

<table>
<tr><th>Adverse Reactions by System</th><th>BOTOX® 24 Units</th><th>Placebo</th></tr>
</table>
</td><td>
• the horizontal lines of rainbow color or the name “Allergan” are not present on the vial label
• the tamper-evident seal is not intact and present on both ends of the carton
• the translucent silver Allergan logo on the seal is not clearly visible or has a black circle with a diagonal line through it (i.e., prohibition sign)
• the U.S. License number 1145 is not present on the vial label and carton

Storage
Unopened vials of BOTOX Cosmetic should be stored in a refrigerator 2° to 8°C (36º to 46ºF). Do not use after the expiration date on the vial. Reconstituted BOTOX Cosmetic should be stored in a refrigerator 2° to 8°C (36º to 46ºF) and administered within 24 hours.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide)
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, 5.7)].

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.
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Category	Korea (Revised:)	US (Revised Feb/2016)

Organ Class	(N=526)	(N=530)
Eye disorders		
Eyelid edema	5 (1%)	0 (0%)

J. Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Treatment with botulinum toxins may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments by inactivating biological activity of the toxin.

In three Crow's Feet Line trials, 916 subjects (517 subjects at 24 U and 399 subjects at 44 U) treated with BOTOX® had specimens analyzed for antibody formation. Among the 916 BOTOX® treated subjects, 14 subjects (1.5%) developed binding antibodies and no subjects (0%) developed the presence of neutralizing antibodies.

The data reflect the subjects 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 antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to BOTOX® with the incidence of antibodies 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 botulinum toxin 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.

K. International Post-Marketing Experience

There have been spontaneous reports of death, sometimes associated with dysphagia,

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Category	Korea (Revised:)	US (Revised Feb/2016)
	pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin [see Precautions 1.Warnings (B, D)]. 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. Angle closure glaucoma has been reported very rarely following BOTOX® treatment for blepharospasm. Lagophthalmos has been reported following BOTOX® injection into the glabellar lines or crow's feet lines.The following adverse reactions have been identified during post-approval use of BOTOX®: abdominal pain; alopecia, including madarosis; anorexia; aspiration pneumonia; brachial plexopathy; denervation/muscle atrophy; diarrhea; diplopia; dry mouth; dysarthria; dysphonia; dyspnea; facial palsy; facial paresis; hyperhidrosis; hypoacusis; hypoesthesia; localized numbness; malaise; muscle weakness; myalgia; myasthenia gravis; nausea; paresthesia; peripheral neuropathy; pruritus; pyrexia; radiculopathy; respiratory depression and/or respiratory failure; skin rash (including erythema multiforme, dermatitis psoriasiform and psoriasiform eruption); strabismus; syncope; tinnitus; vertigo; vision blurred; visual disturbances; vomiting; dry eye, and localized muscle twitching/involuntary muscle contractions. Because these reactions 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 drug exposure. L. AEs from Domestic Post-Marketing surveillance result	

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Category	Korea (Revised:)	US (Revised Feb/2016)
	① No adverse event reported in 4 years Post Marketing Surveillance(PMS) in 55 patients with primary axillary hyperhidrosis. ② Adverse events rate was 2.5% (6/237patients, 7cases) in 237 patients with focal muscle spasticity associated with stroke, 18 years of age or older from PMS for 4 years, and there was a case of headache as adverse reaction its causality with BOTOX® could not exclueded. No SAE was reported. Dyspepsia(2 cases), constipation(1 case), somnolence(1 case) and parkinson's syndrome (1 case) reported as unexpected adverse event. There was no unexpected adverse reaction. ③ Adverse events rate was 1.2% (5/423 patients, 11 cases) in 432 patients with moderate to severe glabellar lines from PMS for 4 years, and the rate of adverse reaction cases its causality with BOTOX® could not excluded is 1.2% (5/423patients, 10 cases), including injection site abnormal (9 cases) and eyelid ptosis(1 case). No SAE was reported. There was no unexpected adverse reaction. 5. General precaution A. This drug contains human albumin derived from human blood. The risk for infectious disease cannot be completely ruled out, which may result from transmission of infectious substance during administration of medicinal products derived from human-blood or plasma. This also applies to pathogenic substance that are yet unknown. To reduce the risk of transmission of these infectious substances, the manufacturing process includes special processes to select donors and donor sites by using an appropriate measurement method, and to inactivate and/or remove infectious substances. B. Asthenia, muscle weakness, dizziness and visual disturbance have been reported after treatment of BOTOX® and could make driving or using machines dangerous. C. Strabismus BOTOX® is ineffective in chronic paralytic strabismus except to reduce antagonist	

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Category	Korea (Revised:)	US (Revised Feb/2016)
	contracture in conjunction with surgical repair. The efficacy of BOTOX® in deviations over 50 prism diopters, in restrictive strabismus, in Duane's syndrome with lateral rectus weakness, and in secondary strabismus caused by prior surgical over-recession of the antagonist is doubtful. In order to enhance efficacy, multiple injections over time may be required. D. Blepharospasm Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles. E. Cervical dystonia Patients who have smaller neck muscle mass and patients who require bilateral injections in to the sternocleidomastoid muscle, have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the risk of dysphagia. Injection into the levator scapulae may increase the risk for upper respiratory infection and dysphagia. F. Pediatric cerebral palsy This drug is a treatment of focal spasticity that has been studied in association with usual standard of care regimen, and is not intended as a replacement for these treatment modalities. It is unlikely that this drug is effective in improving range of motion of a joint that is affected by a permanent contracture. G. Primary axillary hyperhidrosis To rule out potential causes of secondary hyperhidrosis (e.g., hyperthyroidism,	

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Category	Korea (Revised:)	US (Revised Feb/2016)
	pheochromocytoma), medical history, physical examination and special additional tests should be performed. This allows avoiding symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease. H. Upper Limb Spasticity BOTOX® is intended for the treatment of focal spasticity that has been studied in association with usual standard of care regimen. BOTOX® is unlikely to be effective in improving range of motion of a joint that is affected by a fixed contracture. I. Upper Facial Lines (Glabellar lines and Crow's Feet Lines) Use caution when BOTOX® treatment is used in the presence of inflammation at the proposed injection site(s), ptosis, or when excessive weakness or atrophy is present in the target muscle(s). An interval of injection of this drug should not be more frequent than every 3 months, and the lowest effective dose should be used. 6. Drug interactions A. Co-administration with aminoglycoside antibiotics or products that interfere with neuromuscular transmission (tubocurarine-like muscle relaxant) increases the potency of this drug. Continuous co-administration with aminoglycoside antibiotics or spectinomycin is contraindicated. Caution should be applied when using polymyxin, tetracycline, or lincomycin in patients who have received this drug. B. The effect of co-administration with different botulinum neurotoxin serotypes at the same time or for several months has not been known. If different botulinum toxin is administered prior to the resolution of the effect of a previously administered botulinum toxin, neuromuscular weakness may be markedly exacerbated.	

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Category	Korea (Revised:)	US (Revised Feb/2016)
	C. Use of anticholinergic drugs after administration of BOTOX may potentiate systemic anticholinergic effects. 7. Administration in pregnant and breast-feeding women There are no adequate and well-controlled studies or data from postmarketing surveillance on the developmental risk associated with use of Botox in pregnant women. When this drug is injected intramuscularly in pregnant mice and rats during the period of organogenesis, NOEL (No Observed Effect Level) was 4 U/kg, and the injection of high doses (8 or 16 U/kg) led to reductions in fetal body weights and/or delayed ossification. In a dose finding study in rabbits, daily injection of the drug in 0.125 U/kg/day (Days 6~18 of gestation) and 2 U/kg/day (days 6~13 of gestation) produced severe maternal toxicity, abortions, and fetal malformations, and in higher doses led to death of the dams. It appears to be that the rabbits are very sensitive to this drug. If patients become pregnant after administration of this drug, the potential risks including abortion or fetal malformations observed in rabbits should be informed to the patients. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when this drug is administered to nursing women. The use of this drug is not recommended in pregnant or nursing women. 8. Pediatric use Safety and effectiveness of this drug in children below the age of 12 (below the age of 16 for cervical dystonia) have not been established for blepharospasm or strabismus. Safety and effectiveness in children and adolescents below the age of 18 in upper limb spasticity, improving glabellar lines, crow's feet lines, and primary axillary hyperhidrosis have not been studied. 9. **Geriatric use** Of the 1001 patients in placebo-controlled clinical studies of BOTOX for the treatment of	

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Category	Korea (Revised:)	US (Revised Feb/2016)
	upper limb spasticity, 35.3% were 65 or older, and 10.3% were 75 years of age or older. No overall differences in safety were observed between elderly patients and younger patients. In clinical studies of BOTOX® across other indications, no overall differences in safety were observed between elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. *Glabellar Lines* In the two initial glabellar lines clinical studies of BOTOX®, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older. *Crow's Feet Lines* In the two crow's feet lines clinical studies of BOTOX®, the responder rates appeared to be higher for subjects younger than age 65 than for subjects 65 years or older. 10. **Carcinogenesis, mutagenesis, impairment of fertility** Long-term studies in animals have not been conducted to evaluate carcinogenic potential of this drug. 11. **Handling of overdose** The signs and symptoms of overdose are not likely to be clearly present immediately after injection. If an accidental administration or oral ingestion occurs, the person should be medically supervised for several weeks for signs and symptoms of generalized weakness of muscle or muscle paralysis. In the event of overdose or accidental administration, antitoxin can be used if the event is immediately recognized. The antitoxin will not reverse any effect of muscle weakness that is already apparent by the time of antitoxin administration. If the musculature of the oropharynx and esophagus are affected, aspiration may occur	

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Category	Korea (Revised:)	US (Revised Feb/2016)
	which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization. 12. **Storage and handling** The unopened drug should be stored in freezing (-20 ~ -5°) or or in a refrigerator (2~8°). The reconstituted drug can be stored in a refrigerator (2~8°) and should be administered within 24 hours. All vials, including expired vials, or equipment used in direct contact with the drug should be disposed of as medical waste. In cases when deactivation of the toxin is desired (e.g., spills), the use of dilute hypochlorite solution (0.5% or 1%) for five minutes is recommended prior to disposal as medical waste. 13. **Information for patients** Patients should discuss with physician if they have any concern regarding the effectiveness and potential risks of this drug. Caution should be employed for any sign and symptom of adverse reaction. If a patient experiences any difficulty with swallowing, speaking, or breathing or muscle weakness following the treatment, he/she should seek medical help immediately. Adverse reaction may occur within several hours or in several weeks following the treatment. Patients with long-term blepharospasms may have become sedentary. The sedentary patients should be cautioned to resume activity gradually, carefully following the administration of BOTOX®. This drug blocks neuromuscular transmission by binding to acceptor site on motor nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. When this drug is injected intramuscularly at therapeutic doses, this drug causes localized	

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Category	Korea (Revised:)	US (Revised Feb/2016)
	myoparalysis by chemical denervation. When muscle becomes chemically denerved, the muscle becomes weak, and extrajunctional acetylcholine receptors may develop. There is evidence that nerve regeneration may occur, and nerve stimulation transmitted to muscle, thus indicating that 'muscle weakness' is reversible. The paralytic effect of BOTOX® is effective in reducing excessive, abnormal contraction associated with blepharospasm. When injected in the neck muscle, this drug reduces both of objective and subjective symptoms of spasmodic spastic torticollis (cervical dystonia), reduce rotation angle of the head and shoulder prominence, reduce the size and strength of hypertrophic muscle and reduce pain. The presence of antibodies to botulinum toxin type A may reduce the effect of BOTOX® treatment. In clinical studies, one patient with blepharospasm who received 3 doses (total 92 U) of BOTOX® for 6 weeks, and several patients with torticollis who received experimental high doses of BOTOX® (total 300 U and more) during one month developed formation of antibodies, resulting in reduced effectiveness. Thus, BOTOX® should not exceed 200 U in a period of month at any case for the treatment of strabismus, and blepharospasm.	

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[Appendix 1] Status Overview of Post Marketing Surveillance

Type of PMS			Number of Subjects	Progression Status and Future Plan
Post-Marketing Surveillance	General PMS		695	This surveillance was conducted in a way that investigators consecutively enrolled subjects who received Botox® Inj. 50 units and signed the informed consent form from the date of contract until the planned number of subjects to be enrolled was reached. The post marketing surveillance was conducted from 04 Feb 2014 to 03 Feb 2018 and 26 investigators at 26 institutions participated in this study. During the re-examination period, case report forms (CRFs) were collected from a total of 695 subjects. Among these, 667 subjects were included in the safety analysis set and 376 subjects were included in the effectiveness analysis set. During the surveillance period, 667 subjects aged between 18 to 75 with 'moderate to severe lateral canthal lines (crow's feet lines)' were included in the safety analysis set. Among these, 14 AEs occurred in 11 subjects, showing an AE incidence of 1.65%. Of these, there were 1 SAE reported in 1 out of 667 (0.15%) subjects. There were 4 unexpected AEs reported in 3 out of 667 (0.45%) subjects . There were 1 unexpected SAE reported in 1 out of 667 (0.15%) subjects . In the effectiveness analysis based on the investigators' overall evaluation on changes in lateral canthal lines following treatment with the study drug, the study drug was found to be "effective" in 99.73% (375/376 subjects) and "ineffective" in 0.27% (1/376 subjects). For other aspects, there was no specific trend to be compared to previous reports at the time of marketing approval. Botox® Inj. 50 units will be continuously monitored in spontaneous reports or other studies.
	Surveillance for special patient population	Pediatric subjects (< 19 years)	0	Not applicable
		Elderly subjects (≥ 65 years)	36	During the surveillance period, 36 elderly subjects (5.40%) were enrolled and no adverse event was reported in this population.
		Pregnant women	0	No subjects
		Subjects with renal impairment	1	During the surveillance period, 1 subject (0.15%) with renal impairment was enrolled and no adverse event was reported in this population.
		Subjects with hepatic impairment	1	During the surveillance period, 1 subject (0.15%) with hepatic impairment was enrolled and no adverse event was reported in this population.
		Long-term user	0	Not applicable
		Other special subject population	0	Not applicable
Special Surveillance			0	Not applicable
Post-marketing clinical trials			0	Not applicable

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[Appendix 2] Disposition of Subjects

Number of subjects whose CRFs were retrieved: 695

Number of subjects excluded from the safety analysis set: 28

Reason	Number of subjects
Foreign Subjects (not Korean)	10
Duplicated Subjects	1
Subjects who didn't receive BOTOX for this study	5
Follow-up failure	11
Subjects who Violated the usage/dosage	1

Number of subjects included in the safety analysis set: 667

Number of subjects excluded from the effectiveness analysis set : 291

Reason	Number of subjects
Subjects with missing information of overall assessment of change in crow's feet lines by the investigator	277
Subjects receive a subsequent BOTOX injection before overall assessment of change in crow's feet lines by the investigator	1
Subjects collected effectiveness evaluations beyond 3 months after the index BOTOX injection	13

Number of subjects included in the effectiveness analysis set: 376

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[Appendix 3-1] Summary Tabulation of Adverse Drug Reactions in Post Marketing Surveillance

Time / Category	Status until approval	Post-Marketing Surveillance						
		1-1st (2014-02-04 ~2014-08-03)	**1-2nd** (2014-08-04 ~2015-02-03)	**2-1st** (2015-02-04 ~2015-08-03)	**2-2nd** (2015-08-04 ~2016-02-03)	**3rd** (2016-02-04 ~2017-02-03)	**4th** (2017-02-04 ~2018-02-03)	**Total**
Number of study sites	-	0	0	5	6	9	13	26
Number of subjects in the safety analysis set	-	0	0	108	114	152	293	667
Number of subjects with ADRs	-	0	0	0	1	1	0	2
Number of ADRs	-	0	0	0	1	1	0	2
Incidence of ADRs	-	0.00	0.00	0.00	0.88	0.66	0.00	0.30

Type of AEs	Number of subjects with ADRs by AE type(%), [n]							
	Status until approval	**1-1st** (2014-02-04 ~2014-08-03)	**1-2nd** (2014-08-04 ~2015-02-03)	**2-1st** (2015-02-04 ~2015-08-03)	**2-2nd** (2015-08-04 ~2016-02-03)	**3rd** (2016-02-04 ~2017-02-03)	**4th** (2017-02-04 ~2018-02-03)	**Total**
Application site disorders	-	**0(0.00%),[0]**	**0(0.00%),[0]**	**0(0.00%),[0]**	**1(0.88%),[1]**	**1(0.66%),[1]**	**0(0.00%),[0]**	**2(0.30%),[2]**
INJECTION SITE PAIN	-	0(0.00%),[0]	0(0.00%),[0]	0(0.00%),[0]	1(0.88%),[1]	1(0.66%),[1]	0(0.00%),[0]	2(0.30%),[2]

*underline: unexpected adverse drug reactions

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[Appendix 3-2] Summary Tabulation of Serious Adverse Events·Adverse Drug Reactions in Post Marketing Surveillance·Special Surveillance·Post Marketing Clinical Study

Time / Categry	Status until approval	Post-Marketing Surveillance · Special Surveillance · Post-Marketing Clinical Study						
		1-1st (2014-02-04 ~2014-08-03)	1-2nd (2014-08-04 ~2015-02-03)	2-1st (2015-02-04 ~2015-08-03)	2-2nd (2015-08-04 ~2016-02-03)	3rd (2016-02-04 ~2017-02-03)	4th (2017-02-04 ~2018-02-03)	Total
Number of study sites	-	0	0	5	6	9	13	26
Number of subjects in the safety analysis set	-	0	0	108	114	152	293	667
Number of subjects with AEs	-	0	0	0	0	0	1	1
Number of AEs	-	0	0	0	0	0	1	1
Incidence of AEs	-	0.00	0.00	0.00	0.00	0.00	0.34	0.15

Type of AEs	Incidence rate of SAEs and Serious ADRs by AE Type (%), [n]							
	Status until approval	1-1st (2014-02-04 ~2014-08-03)	1-2nd (2014-08-04 ~2015-02-03)	2-1st (2015-02-04 ~2015-08-03)	2-2nd (2015-08-04 ~2016-02-03)	3rd (2016-02-04 ~2017-02-03)	4th (2017-02-04 ~2018-02-03)	Total
Urinary system disorders	-	**0(0.00%),[0]**	**0(0.00%),[0]**	**0(0.00%),[0]**	**0(0.00%),[0]**	**0(0.00%),[0]**	**1(0.34%),[1]**	**1(0.15%),[1]**
RENAL FAILURE ACUTE	-	0(0.00%),[0]	0(0.00%),[0]	0(0.00%),[0]	0(0.00%),[0]	0(0.00%),[0]	1(0.34%),[1]	1(0.15%),[1]

*underline: unexpected serious adverse events · adverse drug reactions

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[Appendix 4] Summary Tabulation of Adverse Event Incidence Status

Refer to the appendix

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[Appendix 5] Table of Adverse Event Case Reports

Refer to the appendix

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[Appendix 6] List of Worldwide Marketing Authorization Status

Refer to the appendix

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[Appendix 7] Line-listing of Serious Adverse Events·Adverse Drug Reactions and Unexpected Adverse Drug Reactions

Refer to the appendix

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[Appendix 8] Listing of Literatuer

No.	Type	Title	Name of Author	Reference
1	Efficacy	Botulinum neurotoxin type A injection of the pelvic floor muscle in pain due to spasticity: A review of the current literature	Bhide AA, Pucci ni F, Khullar V, E lneil S, Digesu GA	International urogynecolog y journal 24.9 (2013): 1429-1434
2	Safety	Flu-like symptoms and associated immunological response following therapy with botulinum toxins	Baizabal-Carvall o JF, Jank ovic J, Feld J	Neurotoxicity research 24.2 (2013): 298-306.
3	Efficacy	long-term efficacy of botulinum toxin in patients with hemifacial spasm	Demir T, Yildiri m S, Demirkiran M	Movement Disorders 28 (2013): S424
4	Efficacy	Botulinum toxin A injections into pelvic floor muscles under electromyographic guidance for women with refractory high tone pelvic floor dysfunction: Three-month follow-up data of an ongoing pilot study.	El-Khawand D, Wehbe S, O'Har e III P, Fariello J, Hoffmann A, Ior io J, et al.	Female pelvic medicine & reconstructive surgery 21.5 (2015): 277-282
5	Safety Efficacy	Long-term efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: An interim analysis	Kennelly M, Dm ochowski R, Eth ans K, Karsenty G, Schulte-Baukl oh H, Jenkins B, et al.	Urology 81.3 (2013): 491-497
6	Efficacy	Use of botulinum toxin in complex regional pain syndrome in the hand	Ovens L, Dewar D	European Journal of Plastic Surgery 36.1 (2013): 37-39
7	Safety Efficacy	Persistent therapeutic effect of repeated injections of onabotulinum toxin A in refractory bladder pain syndrome/interstitial cystitis	Pinto R, Lopes T, Silva J, Silva C, Dinis P, Cruz F	The Journal of urology 189.2 (2013): 548-553.
8	Efficacy	The efficacy of combination therapy with a novel continuous dermal heating monopolar radiofrequency device and botulinum toxin type A for facial contouring: A split-face study	Suh DH, Chang K-Y, Lee S, Kim Y-J, Shin M	Journal of the American Academy of Dermatology 68.4 (2013): AB226
9	Efficacy	Middle airway obstruction in asthma treated with botulinum toxin	Uddin AN, Baxt er M, Raghav S, Low K, Leong P, Holmes P, et al.	Respirology 18 (2013): 25
10	Efficacy	Effect of botulinum-A toxin injection into bulbospongiosus muscle on ejaculatory latency time in male rats	Serefoglu EC, H awley W, Lasker G, Grissom E, Si kka S, Dohanich G, et al	The Journal of Sexual Medicine 9 (2012): 331
11	Efficacy	BTX-A administration to the target muscle affects forces of all muscles within an intact compartment and epimuscular myofascial force transmission	Yucesoy CA, Em re AO, Ates F	Journal of biomechanical engineering 134.11 (2012): 111002

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No.	Type	Title	Name of Author	Reference
12	Efficacy	Botulinum neurotoxin type A in the masseter muscle: Effects on incisor eruption in rabbits	Navarrete AL, Rafferty KL, Liu ZJ, Ye W, Greenlee GM, Herring SW	American Journal of Orthodontics and Dentofacial Orthopedics 143.4 (2013): 499-506
13	Efficacy	Botulinum toxin results in decreased proliferation and apoptosis in the rat bulbous spongiosum	Mandava SH, Abd Elmageed Z, Lasker G, Gokce A, Trost L, Kadowitz P, et al.	Andrology 1 (2013): 75
14	Efficacy	Botulinum toxin type A therapy in migraine: Preclinical and clinical trials	Shao Y-F, Zhang Y, Zhao P, Yan W-J, Kong X-P, Fan L-L, et al.	Red Crescent Medical Journal 15.10 (2013).
15	Safety	Angle-closure glaucoma following periorbital botulinum toxin injection	Zheng L, Azar D	Clinical & experimental ophthalmology 42.7 (2014): 690-693
16	Safety	Adverse testicular effects of Botox® in mature rats	Breikaa RM, Mosli HA, Nagy A A, Abdel-Naima AB	Toxicology and applied pharmacology 275.2 (2014): 182-188
17	Efficacy	The role of neurotoxins in the periorbital and midfacial areas	Erickson BP, Lee WW, Cohen J, Grunebaum LD	Facial Plastic Surgery Clinics 23.2 (2015): 243-255
18	Safety Efficacy	Botulinum toxin in masticatory muscles of the adult rat induces bone loss at the condyle and alveolar regions of the mandible associated with a bone proliferation at a muscle enthesis	Kun-Darbois JD, Libouban H, Chappard D	Bone 77 (2015): 75-82.
19	Efficacy	Effect of Botulinum Toxin Type A on Differentiation of Fibroblasts Derived from Scar Tissue	Hii Sun Jeong; Byeong Ho Lee; Ha Min Sung; S ook Young Park; Duk Kyun Ahn; Min Su Jung; In Suck Suh	Plastic and reconstructive surgery 136.2 (2015): 171e-178e
20	Safety	Ultrasound-guided botulinum toxin type A salivary gland injection in children for refractory sialorrhea: 10-year experience at a large tertiary children's hospital	Lungren MP, Halula S, Coyne S, Sidell D, Racad io JM, Patel MN	Pediatric neurology 54 (2016): 70-75
21	Efficacy	Influence of onabotulinumtoxin A on testes of the growing rat	Breikaa RM, Mosli HA, Abdel-Naim AB	Journal of biochemical and molecular toxicology 30.12 (2016): 608-613.
22	Efficacy	Adverse testicular effects of Botox in mature rats	Breikaa RM, Mosli HA, Nagy A A, Abdel-Naim AB	Toxicology and applied pharmacology 275.2 (2014): 182-188

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[Appendix 9] Summary of Literature

<table>
<tr><td>DIN·frequency of report</td><td>1</td><td></td><td>Report date
Not applicable</td><td>First report obtainment date
Not applicable</td><td colspan="2">Division of new drug, etc.
Not applicable</td><td>Note (this space should be left blank)</td></tr>
<tr><td>General name</td><td colspan="2">Clostridium Botulinum Toxin Type A</td><td rowspan="2">Publication status of study reports</td><td rowspan="2">Not applicable</td><td rowspan="2">Publishing country</td><td rowspan="2"></td></tr>
<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="5">Botulinum neurotoxin type A injection of the pelvic floor muscle in pain due to spasticity: A review of the current literature

The role of muscle spasm is not a new concept in the genesis of pain. Botulinum neurotoxin type A (BoNTA) has been successfully employed in a variety of muscular and inflammatory conditions. The aim of our study was to review the published literature on the role of BoNTA injection of the pelvic floor muscle in the management of women with chronic pelvic pain (CPP). A systematic search of the literature published up to June 2012 on the use of BoNTA in the treatment of female pelvic floor muscle spasm was carried out using relevant search terms in MEDLINE and EMBASE databases. The results were limited to full-text English language articles. Relevant trials as well as relevant reviews were selected and analyzed by two independent reviewers. Five studies (2 case reports, 1 prospective pilot study, 1 retrospective study and 1 randomised double-blind placebo controlled study) were included in this systematic review. Overall, BoNTA has shown to be beneficial in relieving CPP related to pelvic floor spasm. The role of BoNTA as a treatment of CPP has been recognized for more than 10 years. Although data are still scarce preliminary results are encouraging. BoNTA is an attractive option for refractory CPP related to pelvic floor muscle spasm, but further studies using validated and reproducible outcome measures are needed, to establish its effectiveness, safeness, technique, optimal dosage, and duration of symptom relief</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="4">Opinions of the company</td><td colspan="3">Future correspondence</td></tr>
<tr><td colspan="4">This systematic review reports that BoNTA has been used successfully for the treatment of CPP. However, the complete benefit:risk profile of BoNTA for this indication has not been established, and currently this is not an approved indication for BOTOX®.</td><td colspan="3">Not applicable</td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="5">Flu-like symptoms and associated immunological response following therapy with botulinum toxins

We aimed to define the frequency and risk factors associated with flu-like symptoms (FLS) and other systemic symptoms following treatment with botulinum toxins (BoNT) and correlate them with the immunological response as determined by blood cytokines. The study involved prospective clinical and serological evaluation for cytokine analysis in patients receiving BoNT for movement disorders. We interviewed 218 patients about FLS following BoNT injections and prospectively studied 117 patients (females 67.5 %; mean age 59.74 ± 12.39 years) treated with BoNT in a total of 143 treatment cycles. While no patient reported any FLS at baseline, the symptom complex was subsequently reported in 19 patients (16.3 %) and in 20 (14 %) treatment cycles, with at least one systemic symptom reported in 49 (42 %) patients in 59 (41.3 %) treatment cycles. FLS and at least one symptom were reported more frequently by women (P = 0.006 and P = 0.049, respectively) and by younger patients: 55.6 versus 61.7 years (P = 0.022). Although the symptoms were usually considered mild, they were rated as moderate to serious after 18 (12 %) cycles. The following interleukins showed increased levels at 7–10 days after the BoNT injections: IL-1b, IL-8, GROa, eotaxin, MCP-1 and 2, RANTES, TARC, and inducible protein 10 (IP10), but only the latter showed significantly increased levels in patients with FLS: 69 versus 3 pg/ml (P = 0.007). FLS and other systemic symptoms occur after about 14 % of treatment visits in patients receiving BoNT. IP10 levels correlate with the presence and severity of FLS.</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="4">Opinions of the company</td><td colspan="3">Future correspondence</td></tr>
<tr><td colspan="4">a listed event in the BOTOX® CCDS for the indications of cervical dystonia, adult poststroke spasticity, and spasmodic dysphonia. These authors found that flu-like symptoms are reported in patients treated with botulinum toxin products, including BOTOX®.</td><td colspan="3">Not applicable</td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="5">long-term efficacy of botulinum toxin in patients with hemifacial spasm

Objective: In this study, we aimed to investigate long-term efficacy and side effects of botulinum toxin A in patients with hemifacial spasm (HFS) who were followed for as long as 16 years in our neurology department.
Background: Intermittent injections of botulinum toxin A has a great importance in treatment of patients with HFS. It is a safe and efficacious treatment. However, there are a few studies with long term efficacy results for more than 10 years.
Methods: Patients with HFS that were followed in our movement disorders unit between 1995 and 2012 were screened. Patients with a follow-up period of at least 1 year were included in the study. Age at onset, duration of disease, follow-up period, the affected muscles, dosage of botulinum toxin A for each injection, the frequency, the number and the site of injections, efficacy and side effects were evaluated.
Results: Thirty-one women and 29 men were included in the study. The mean age at onset was 47 (23-78) years; mean duration of disease was 8 (1-23) years. Follow-up period of 47% of cases were at least 4 years and mean follow-up period was 50 months (12-192). While mean initial dosage of botulinum toxin A was 26.95U (10-45), last dosage was 29.33U (5-62). Effect was evident in all patients and did not lose its efficacy through the years with repeated injections. Although permanent facial assymmetry [sic] was observed in a very few cases, side effects were rare and for short-term.
Conclusions: Botulinum toxin injections can be used for many years in patients with HFS without any safety concerns. It is still the first choice of treatment in HFS.</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="4">Opinions of the company</td><td colspan="3">Future correspondence</td></tr>
<tr><td colspan="4">Of note hemifacial spasm in patients 12 years and older is a labeled indication for BOTOX®. This study is worthy of note due to the long follow-up period reported.</td><td colspan="3">Not applicable</td></tr>
</table>

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DIN·frequency of report	4		**Report date** Not applicable	**First report obtainment date** Not applicable	**Division of new drug, etc.** Not applicable	**Note (this space should be left blank)**
General name	Clostridium Botulinum Toxin Type A		**Publication status of study reports**	Not applicable	**Publishing country**	
Brand name (manufacturer's name)	Botox Inj. 50 units (Allergan Korea Ltd.)					
Abstract	**Botulinum toxin A injections into pelvic floor muscles under electromyographic guidance for women with refractory high tone pelvic floor dysfunction: Three-month follow-up data of an ongoing pilot study.** **Introduction and Objectives:** Our objective is to determine the efficacy of electromyography (EMG) guided botulinum toxin A (BT-A) injections in treating pelvic pain and improving QoL in women with refractory high tone pelvic floor dysfunction (HTPFD). **Methods:** This is an interim analysis of an ongoing prospective pilot cohort study of women with chronic pelvic pain and HTPFD who have failed conventional therapy. Enrollment started in January 2011. BT-A injections (up to 300 units) were done using needle EMG guidance to localize spastic pelvic floor muscles (PFM). All patients who have completed 12 weeks follow-up (n=14) were analyzed. Data was collected at baseline, 4, 8, 12, and 24 weeks after injections. This included demographics, visual analog scores (VAS) for pain and dyspareunia, validated questionnaires for symptoms, QoL, and sexual function, Global Response Assessment (GRA) scale for pelvic pain, digital exam of PFM for tone and tenderness, and vaginal manometry. Side effects were also recorded. **Results:** Mean age was 36.6 years (SD.+-.10.9, range 22-52), mean body mass index 24.7 (3.4). Overall, 71% of subjects reported improvement on GRA at 4 weeks, and 79% at 8 and 12 weeks post injection, compared to baseline. Of the 10 subjects who were sexually active at baseline, 80%, 70%, and 60% reported less dyspareunia at 4, 8, and 12 weeks respectively. Sexual dysfunction as measured by the Female Sexual Distress Scale (FSDS) significantly improved at 8weeks (25.36, p=0.025) and 12 weeks (25.93, p=0.028) compared to baseline (33.14). Short Form 12 (SF-12) showed improved QoL in the physical composite score both at 4 (43 vs 37.2, p=0.014) and 12 weeks (43.5 vs 37.2, p=0.041), and in the mental composite score at 12 weeks (45.69 vs 38.24, p=0.03). Digital assessment of PFM (on a scale from 0 to 4) showed decreased tenderness on all visits (mean of 1.79, p=0.01; 1.35, p=0.001; 1.46, p=0.004) compared to baseline (2.49). Reported post-injection side effects included constipation (50%), worsening of pre-existing stress urinary incontinence (SUI) and fecal incontinence (7%), and new onset SUI (14%). **Conclusions:** EMG guided BT-A injection into PFM could be beneficial for women with refractory HTFPD who have failed conservative therapy.					**Remarks on 'Precaution for use' and references, etc.** Not applicable
Opinions of the company				**Future correspondence**		
This interim analysis of an ongoing prospective pilot cohort study of 14 women with chronic pelvic pain and HTPFD who have failed conventional therapy, who have completed 12 weeks follow-up shows that EMG guided BT-A injection into PFM could be beneficial for women with refractory HTFPD who have failed conservative therapy. However, this study is not placebo-controlled. Also, a complete benefit/risk profile has not been established in this setting.				Not applicable		

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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="5">Long-term efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: An interim analysis

Objective: To evaluate the long-term efficacy and safety of repeat onabotulinumtoxinA injections in patients inadequately managed by anticholinergics for urinary incontinence (UI) due to neurogenic detrusor overactivity.
Materials and Methods: Patients who completed either of 2 preceding phase III studies were offered entry into an extension study and received repeat onabotulinumtoxinA 200 U or 300 U. The data were integrated across the phase III and ongoing extension studies. The present interim analysis included all patients who received ≥ 1 onabotulinumtoxinA treatment. The data were analyzed by treatment cycle (cycles 1-5). The primary assessment was the change from baseline in UI episodes/wk at 6 weeks after each treatment. Additional assessments included ≥ 50% and 100% reductions in UI episodes, volume/void, Incontinence Quality of Life responses, and adverse events.
Results: A total of 387, 336, 241, 113, and 46 patients received 1, 2, 3, 4, and 5 onabotulinumtoxinA treatments, respectively. The UI episodes/wk were consistently reduced compared with baseline after repeated onabotulinumtoxinA treatment (-22.7, -23.3, -23.1, -25.3, and -31.9 for the 200-U onabotulinumtoxinA group in cycles 1-5). The proportion of patients reporting ≥ 50% and 100% ("dry") reductions from baseline in UI episodes at week 6 ranged from 73%-94% and 36%-55%, respectively. Increases in the mean volume/void (mean increase >130 mL) and improvements in quality of life were also observed after repeat treatment. The most common adverse events were urinary tract infections and urinary retention, with no change in the adverse event profile over time.
Conclusion: The results of our study have shown that repeated onabotulinumtoxinA treatments provide sustained reductions in UI episodes and increases in the volume/void and quality of life in patients with neurogenic detrusor overactivity and UI who were inadequately managed by anticholinergics, with no new safety signals.</td><td rowspan="3">Remarks on 'Precaution for use' and references, etc.
1.Warnings
J. Pulmonary Effects of BOTOX® in Adult Patients with Compromised Respiratory Status Treated for Upper Limb Spasticity or for Neurogenic Detrusor Overactivity</td></tr>
<tr><td colspan="4">Opinions of the company</td><td colspan="2">Future correspondence</td></tr>
<tr><td colspan="4">In this publication of interim results from Allergan-sponsored study 191622094, the authors report that onabotulinumtoxinA has been proven effective in the long-term treatment of urinary incontinence with no new safety signals identified</td><td colspan="2">Not applicable</td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="5">Use of botulinum toxin in complex regional pain syndrome in the hand

Abstract: This is the first report of the use of botulinum toxin injected into the hand to treat complex regional pain syndrome (CRPS). Botulinum toxin has been shown to improve pain in Raynaud's syndrome, carpal tunnel syndrome, and CRPS of the lower limb. Botulinum toxin has also been shown to act on pain neurotransmitters directly. A [redacted] man was referred to us with bilateral CRPS after falling onto his hands. Fifty units of BOTOX® were injected into the carpal tunnel and 50 units around the digital neurovascular bundles of the left non-dominant hand. Hand assessments were performed before injection, and weekly for 6 weeks post-injection. The dominant hand acted as a control. A steady improvement of power grip strength in the left hand was shown. Power in his left hand was greater than the right, despite him being right handed. Total active movement did not change significantly. He felt the injection was beneficial. Botulinum toxin may have improved the signs and symptoms of CRPS in the hand due to its combined effect on the vascular and nervous systems. Botulinum toxin may block the self-perpetuation cycle of pain and sympathetic stimulation by blocking neurotransmitters and warrants further studies on CRPS.</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="4">Opinions of the company</td><td colspan="3">Future correspondence</td></tr>
<tr><td colspan="4">In this case report, botulinum toxin was shown to be effective in treating CRPS. It is postulated that botulinum toxin may block the sympathetic stimulation. However, a complete benefit:risk profile is not established for the use of BOTOX® in treating CRPS.</td><td colspan="3">Not applicable</td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Persistent therapeutic effect of repeated injections of onabotulinum toxin A in refractory bladder pain syndrome/interstitial cystitis

Purpose: We evaluate the efficacy and safety of repeated intratrigonal injections of onabotulinum toxin A in patients with bladder pain syndrome/interstitial cystitis.

Materials and methods: This is a single center, long-term, prospective study in which 16 women with bladder pain syndrome/interstitial cystitis refractory to standard treatment received 4 consecutive intratrigonal injections of onabotulinum toxin A. Onabotulinum toxin A (100 U) was injected under cystoscopic control in 10 trigonal sites, each receiving 10 U in 1 ml saline. General anesthesia was used in all treatments. Re-treatment was allowed 3 months after injection. Outcome measures included pain visual analog scale (0-10), O'Leary-Sant score, a 3day voiding chart and a quality of life questionnaire at the first month and every 3 months after each injection. Voiding dysfunction and urinary tract infections were assessed at 2 weeks and every 3 months afterward. Treatment duration was determined when patients requested another injection.

Results: Mean ± SD patient age was 41.8 ± 12.5 years. At baseline pain score was 5.9 ± 1.8, O'Leary-Sant score 28.8 ± 6.3, urinary frequency 16.4 ± 5.3, mean voided volume 112 ± 42 ml and quality of life 5 ± 0.9. Mean decrease in pain score, O'Leary-Sant score, urinary frequency and mean increase in voided volume and quality of life were similar after each treatment. Individual symptom relief lasted 6 to 12 months with an average duration of 9.9 ± 2.4 months. There were no cases of voiding dysfunction. Five patients had noncomplicated urinary tract infections.

Conclusions: Symptomatic improvement of bladder pain syndrome/interstitial cystitis persists in a repeated intratrigonal injection program of 100 U onabotulinum toxin A. Time to request re-treatment remained stable. Adverse events were mild, without voiding dysfunction requiring intermittent catheterization.</td><td>Remarks on 'Precaution for use' and references, etc.
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<tr><td colspan="5">Opinions of the company</td><td colspan="2">Future correspondence</td><td rowspan="2"></td></tr>
<tr><td colspan="5">Patients with bladder pain syndrome/interstitial cystitis who were treated with onabotulinumtoxinA 100 U achieved symptomatic improvement of bladder pain syndrome and interstitial cystitis with mild adverse events and without persistent urinary retention. However, this study is not placebo-controlled. Also, the complete benefit:risk profile of onabotulinumtoxinA is not established in this setting.</td><td colspan="2">Not applicable</td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">The efficacy of combination therapy with a novel continuous dermal heating monopolar radiofrequency device and botulinum toxin type A for facial contouring: A split-face study

Background: Botulinum toxin type A can produce dramatic improvements in patients with benign masseteric hypertrophy for Asian women. The use of botulinum toxin type A for lower facial contouring is a very popular cosmetic procedure in Korea. However, in some cases after this treatment, the laxity of mid-face could be occurred as masseter muscle mass decreases.

Objective: The purpose of this study was to compare botulinum toxin type A monotherapy with botulinum toxin type A plus a novel nonablative 4-MHz monopolar radiofrequency treatment.

Methods: Thirteen female subjects ranging from 21 to 48 years of age with skin types III to V were enrolled and received single session of botulinum toxin type A (BOTOX®) injection on both sides of faces. 25 to 30 U of BOTOX® per side was injected at 3 points into the prominent portions of the mandibular angle and followed by radiofrequency (The Surgitron Dual Frequency RF S5 with Pelleve handpiece [Ellman International, Inc, Oceanside, NY]) treatment on 1 side of cheek. Additional 2 sessions of radiofrequency treatment were done in all subjects at 3-week intervals.

Results: The serial photographs and patient subjective evaluation showed an obvious facial change 2 to 6 months after treatment. After the treatments, surface smoothness and skin tension of the botulinum toxin plus radiofrequency treatment is significantly improved than botulinum toxin monotherapy. No significant side effects were observed.

Conclusion: The monopolar radiofrequency plus botulinum toxin treatment appeared superior to botulinum toxin monotherapy in aspect of both efficacy and patients satisfaction. Especially it is more effective for rounded and drooped lower face.</td><td>Remarks on 'Precaution for use' and references, etc.
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<tr><td colspan="5">Opinions of the company</td><td colspan="2">Future correspondence</td><td></td></tr>
<tr><td colspan="5">In this small study, the monopolar radio frequency with botulinum toxin treatment appeared more effective to botulinum toxin monotherapy for the treatment of benign masseteric hypertrophy for the outcome of rounded and drooped lower face. However, complete benefit/risk profile has not been established in this indication, especially with monopolar radio frequency with botulinum toxin.</td><td colspan="2">Not applicable</td><td></td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Middle airway obstruction in asthma treated with botulinum toxin

Background: Vocal cord dysfunction (VCD) causes middle airway obstruction, may coexist with asthma and contributes to severe breathlessness. Botulinum toxin causes temporary paralysis of muscle and may be an effective local treatment for VCD reducing asthma symptoms.

Methods: We used unilateral laryngeal/vocal cord injection with botulinum toxin in 7 patients (18 injections) with intractable dyspnoea, VCD and asthma resistant to optimized treatment. Two methods of injection were compared: (i) blind injection under EMG guidance and (ii) injection under direct vision and general anaesthetic. Symptoms and other responses after botulinum toxin were assessed using the asthma control test (ACT), CT larynx and spirometry and side-effects were noted.

Results: Both blind and direct injection under general anaesthetic improved ACT scores (blind, n = 10; p = 0.005 and direct, n = 8; p = 0.009). There was no difference in effect between the methods but the direct method trended to a greater improvement in scores (mean direct 6.1 4.5 versus blind 4.0 3.4; p = 0.28). In the direct group 5/8 patients had an improvement in ACT score 5 versus 4/10 in the blind group (p = 0.07). VCD detected by CT larynx also gave indications that treatment with botulinum toxin improved airway function. Spirometry was overall little altered. Side-effects were mild, chiefly transient dysphonia and dysphagia.

Conclusions: This case series provides preliminary evidence that local injection of botulinum toxin may be an effective treatment improving asthma control in disease complicated by VCD. Further mechanistic studies and a randomized controlled trial of treatment are merited.</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="5">Opinions of the company</td><td colspan="2">Future correspondence</td><td></td></tr>
<tr><td colspan="5">The treatment of asthma is not an appoved indication or under investigation for BOTOX® / BOTOX® COSMETIC. The clinical relevance of these data for this small group of 7 patients remains to be determined.</td><td colspan="2">Not applicable</td><td></td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Effect of botulinum-A toxin injection into bulbospongiosus muscle on ejaculatory latency time in male rats

Objective: Bulbospongiosus muscle (BSM) is involved in ejaculation and local administration of the Botulinium-A Toxin (Btx-A) has been shown to impact muscle contractions. The current study was conducted to examine the effect of Btx-A injection into the BSM on the ejaculatation latency of male rats.

Methods: After confirming sexual behavior in 33 male Long-Evans rats with sexually receptive females, those that exhibited the entire repertoire of sexual behaviors received an additional 4 sexual experiences over the course of the following week in which all sexual behaviors were recorded by trained observers. On the day after their last experience, rats were lightly anesthetized, and received an injection of either 0.5 (n = 11), or 1 unit (n = 11) of Btx-A, or saline vehicle (n = 11). Btx-A was delivered bilaterally in 0.1 ml of saline vehicle injected percutaneously into the BSM. Two days after treatment, sexual behaviors were re-examined over the course of the following week on 4 separate occasions. The latency to ejaculation was recorded by trained observers blind to the conditions.

Results: Relative to pre-treatment ejaculation latencies, bilateral injection of saline into the BSM did not impact ejaculation latencies (402.3 ± 220.1 sec vs. 453.8 ± 275.2 sec, P = 0.53); however, rats treated with either 0.5 or 1 unit Btx-A exhibited significantly longer latencies to achieve ejaculation relative to pre-treatment performance (357.9 ± 237.3 sec vs. 590.2 ± 306 sec, P = 0.04 and 302.8 ± 171.0 sec vs. 668.0 ± 376.8 sec, P = 0.013, respectively). Btx-A did not impact the ability to achieve mount or intromission.

Conclusion: These results demonstrate that Btx-A injection into the BSM is a safe and effective treatment which can lengthen the latency time to ejaculate in rats without suppressing sexual behavior. Further studies are required to evaluate the therapeutic concept of this drug in premature ejaculation (PE) patients.</td><td>Remarks on 'Precaution for use' and references, etc.
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<tr><td colspan="5">Opinions of the company</td><td colspan="2">Future correspondence</td><td></td></tr>
<tr><td colspan="5">The authors demonstrated that botulinum toxin A injected into the bulbospongiosus muscle at 0.5 or 1.0 units delayed ejaculation in male Long-Evans rats. Allergan has an ongong phase 2a study (191622-133) in patients with PE to explore the potential efficacy of BOTOX® for the treatment of PE.</td><td colspan="2">Not applicable</td><td></td></tr>
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General name	Clostridium Botulinum Toxin Type A		**Publication status of study reports**	Not applicable	**Publishing country**	
Brand name (manufacturer's name)	Botox Inj. 50 units (Allergan Korea Ltd.)					
Abstract	**BTX-A administration to the target muscle affects forces of all muscles within an intact compartment and epimuscular myofascial force transmission** **Abstract:** Measurement of forces of mono- and bi-articular muscles of an entire intact muscle compartment can allow for a comprehensive assessment of the effects of Botulinum toxin type A (BTX-A) both at and beyond the injection site, and in conditions close to those *in vivo*. The goal was to test the hypotheses that BTX-A affects (1) the forces of not only the injected but also the noninjected muscles of the compartment, and (2) epimuscular myofascial force transmission (EMFT). Two groups of Wistar rats were tested: Control (no BTX-A injected) and BTX (0.1 units of BTX-A were injected exclusively to the mid-belly of the tibialis anterior [TA]). Isometric forces were measured simultaneously at the distal tendons of the TA at different lengths, the restrained extensor digitorum longus (EDL) and the extensor hallucis longus (EHL) muscles and at the proximal tendon of EDL. Five days post-injection, BTX-A did affect the total forces of all muscles significantly: (1) The TA force decreased differentially (by 46.6%-55.9%) for most lengths such that a significant negative correlation was found between force reductions and increased muscle length. The maximum TA force decreased by 47.3%. However, the muscles length range of force production did not change significantly. (2) Distal and proximal EDL forces decreased (on average by 67.8% and 62.9%, respectively). (3) The EHL force also decreased (on average by 9.2%). The passive forces of only the TA showed a significant increase at higher lengths. EMFT effects were shown for the control group: (1) at the shortest TA lengths, the EDL proximo-distal force differences were in favor of the distal force, which was reversed at higher lengths. (2) the EHL force measured at the shortest TA length decreased (by 34%) as a function of TA lengthening. After BTX-A exposure, such EMFT effects disappeared for the EDL, whereas they remained as profound for the EHL. Exposure to BTX-A does affect forces of all muscles operating in an intact compartment. For the BTX-A injected muscle, the reduction in muscle force becomes less pronounced at higher muscle lengths. BTX-A also has effects on EMFT, however, these effects are not uniform within the anterior crural compartment. Decreased forces of the noninjected synergistic muscles suggest the presence of unintended additional effects of BTX-A both for the targeted distal joint and for the nontargeted proximal joint.					**Remarks on 'Precaution for use' and references, etc.** Not applicable
Opinions of the company				**Future correspondence**		
The significance of this publication is that the authors assessed muscle force to determine the local spread of BTX-A (BOTOX®) to non-injected muscles within a muscle fascial compartment. The findings suggest that diffusion occurs preferentially along the muscle within *its muscle compartment and that fascial planes limit diffusion of toxin. This is consistent with what is known about local tissue spread of BTX-A injected intramuscularly, based on internal studies on the diffusion characteristics of BTX-A administered IM*				Not applicable		

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into the left gastrocnemius in rat and non-human primate, and published clinical studies in human.		

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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Botulinum neurotoxin type A in the masseter muscle: Effects on incisor eruption in rabbits

Introduction: Botulinum neurotoxins are responsible for the paralytic food poisoning, botulism. Commercial formulations such as botulinum neurotoxin type A are increasingly used for various conditions, including cosmetic recontouring of the lower face by injection of the large masseter muscles. The paralysis of a major muscle of mastication lowers occlusal force and thus might affect tooth eruption. The purpose of this study was to investigate the effects of unilateral masseter muscle injection of botulinum neurotoxin type A on the rate of eruption of incisors in a rabbit model. We hypothesized that the teeth would overerupt in an underloaded environment.

Methods: Forty rabbits were injected with either botulinum neurotoxin type A or saline solution in 1 masseter muscle. Mastication and muscle force production were monitored, and incisor eruption rate was assessed by caliper measurement of grooved teeth.

Results: The injection of saline solution had no effect. The masseter muscle injected with botulinum neurotoxin type A showed a dramatic loss of force 3 weeks after injection despite apparently normal mastication. Incisor eruption rate was significantly decreased for the botulinum neurotoxin type A group, an effect attributed to decreased attrition.

Conclusions: This study has implications for orthodontics. Although findings from ever-growing rabbit incisors cannot be extrapolated to human teeth, it is clear that botulinum neurotoxin type A caused a decrease in bite force that could influence dental eruption.</td><td>Remarks on 'Precaution for use' and references, etc.
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<tr><td colspan="4">Opinions of the company</td><td colspan="3">Future correspondence</td><td></td></tr>
<tr><td colspan="4">Botulinum neurotoxin type A (BoNT/A) treatment of the masseter muscle does not negatively impact effective mastication in rabbits, an observation also made in humans. BoNT/A affects incisor eruption in rabbits; however, changes in dentition have not been reported in humans. The clinical safety implication of this early pre-clinical research finding is still unknown.</td><td colspan="3">Not applicable</td><td></td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Botulinum toxin results in decreased proliferation and apoptosis in the rat bulbous spongiosum

Introduction and Objectives: Botulinum toxin is commonly utilized inurologic practice for several indications, including overactive bladder, neurogenic bladder and detrusor-sphincter dyssynergia, etc. Although recent studies have described botulinum toxin migration following intramuscular injection, minimal data is currently available regarding the effects of drug migration on adjacent tissues. We sought to examine whether the injection of botulinum toxin in rat bulbous striated muscle affects the mitochondrial protein Sirt3, and regulates intrinsic mitochondrial apoptosis and cell death.

Methods: 14 male Sprague Dawley rats were divided into 3 groups and treated with single injection into the bulbospongiosus muscle: controls (saline), low dose (botulinum toxin A, 0.5 units), and high dose (botulinum toxin A, 1.0 unit). Rats were subsequently sacrificed at 4 weeks and the bulbospongiosus muscle harvested. Various analyses were performed to evaluate expression of Sirt3 (Western blot), α-tubulin (Western blot), NADPH oxidase levels (lucigenin chemiluminescence), and tissue apoptosis (TUNEL assay).

Results: Rats treated with botulinum toxin A demonstrated decreased levels of Sirt3 in the bulbospongiosus muscle compared to controls, with the high dose group exhibiting the lowest expression. Using a quantitative Sirt3/α-tubulin ratio, the high dose group experienced the lowest Sirt3 protein levels (30%), compared to low dose (75%) and controls (100%), $p<0.05$. NADPH oxidase activity was significantly increased in both the low dose (800 relative light units [RLU]) and high dose (1500 RLU) groups compared to controls (400 RLU). Using TUNEL categorical scores, apoptosis was identified more frequently in low dose (10) and high dose (15) treatment groups, compared to controls (5).

Conclusion: Injection of botulinum toxin A into the rat bulbospongiosus muscle results in decreased Sirt3 expression and increased NADPH oxidase activity that may affect ATP production and cause oxidative stress. This results in increased tissue destruction and cell death.</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="5">Opinions of the company</td><td colspan="2">Future correspondence</td><td></td></tr>
<tr><td colspan="5">The significance of this publication is that the authors have shown that botulinum toxin A injection into the bulbospongiosum muscle of rats results in decreased SIRT3 expression and increased NADPH-oxidase activity. Decreased SIRT3 expression and increased NADPH activity could affect ATP production and potentially increase oxidative stress. The clinical safety implication of this early pre-clinical research finding is still unknown.</td><td colspan="2">Not applicable</td><td></td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="5">Botulinum toxin type A therapy in migraine: Preclinical and clinical trials

Background: Botulinum toxin type A (BTX-A) has been reported to be effective for the therapy for migraine. The purpose of this study was to investigate the effect of BTX-A on the immunoreactive levels of calcitonin gene-related peptide (CGRP) and substance P (SP) in the jugular plasma and medulla oblongata of migraine in rats induced by nitroglycerin (NTG), and then to evaluate and compare the effectiveness of fixed (muscle)-sites and acupoint-sites injection of BTX-A for migraine therapy of patients in a randomly controlled trial extending over four months.

Materials and Methods: Rats with NTG-induced migraine were subcutaneously injected with vehicle or BTX-A (5 U/kg or 10 U/kg bodyweight). CGRP- and SP-like immunoreactivity (CGRP-LI and SP-LI) were determined by radioimmunoassay. In clinical trials, sixty patients respectively received BTX-A (2.5 U each site, 25 U per patient) at fixed-sites (group F, n = 30) including occipitofrontalis, corrugator supercili, temporalis and trapezius or at acupoint-sites (group A, n = 30) including EX-HN3, EX-HN5, GV20, GB8, GB20 and BL10.

Result: Local BTX-A injection suppressed NTG-induced CGRP-LI and SP-LI levels in jugular plasma and oblongata. BTX-A injection for both groups with migraine significantly reduced the attack frequency, intensity, duration and associated symptoms. The efficacy of BTX-A for migraine in group A (93% improvement) was more significant than that in group F (83% improvement) (P 0.01).

Conclusions: The evidence that BTX-A decreases NTG-induced CGRP-LI and SP-LI levels in trigeminovascular system suggests that BTX-A attenuates migraine by suppression of neuropeptide release. BTX-A injections for migraine at acupoint-sites and fixed-sites are effective. Acupoint-sites BTX-A administration shows more efficacy for migraine than fixed-sites application.</td><td>Remarks on 'Precaution for use' and references, etc.
1. Warnings
4. Adverse Events
D. Cervical dystonia
F. Primary axillary hyperhidrosis
G. Upper Limb Spasticity
L. AEs from Domestic Post-Marketing surveillance result</td></tr>
<tr><td colspan="4">Opinions of the company</td><td colspan="2">Future correspondence</td><td></td></tr>
<tr><td colspan="4">The authors demonstrated that two hours after NTG treatment, BTX-A administration decreased CGRP-LI and SP-LI levels in jugular plasma and oblongata, presumably by inhibition of acetylcholine exocytosis. These findings suggest the possibility that the sensory-specific effect of BTX-A might occur through inhibition of sensory neuropeptide vesicle release via a SNAP-mediated mechanism, similar to the blockade of acetylcholine release in motor neurons. In the clinical portion of the study, Acupoint-sites and fixed-sites injection of BTX-A for migraine were able to significantly reduce attack frequency, intensity, duration, and associated symptoms.</td><td colspan="2">Not applicable</td><td></td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Angle-closure glaucoma following periorbital botulinum toxin injection

There is not 'abstract' about this literature in PSUR</td><td>Remarks on 'Precaution for use' and references, etc.
4. Adverse Events
C. Blepharospasm
K. International Post-Marketing Experience

5. General precaution
D. Blepharospasm</td></tr>
<tr><td colspan="5">Opinions of the company</td><td colspan="3">Future correspondence</td></tr>
<tr><td colspan="5">This letter to editor refers to a patient who had a family history of angle closure glaucoma but no baseline visual field or gonioscopy or biomicroscopy examinations. She presented with bilateral evidence of angle closure glaucoma (more on the left eye). This patient received botulinum toxin (unknown doses, unknown indication, unspecified sites of injection, and unspecified side of injection) every 3-4 months for the past "several years". The theoretical basis for an impact on the ganglionic cholinergic inhibition of the pupillary sphincter resulting in angle closure glaucoma had been suggested through an animal study after "periocular or retrobulbar" injections, which are not necessarily comparable to the IM injections for cosmetic indications mechanism of action. However, there is neither support for a diffusion mechanism relevant to cosmetic injections nor available baseline information from this patient to support further conclusions. The CCDS, in section 13.2 Post Marketing Experience, states that "Angle closure glaucoma has been reported very rarely following BOTOX treatment for blepharospasm", and in Section 7 Warnings and Precautions for Blepharospasm, it states "Because of the anticholinergic activity of botulinum toxin, caution should be exercised when treating patients at risk for angle closure glaucoma, including patients with anatomically narrow angles." Allergan will continue to monitor the occurrence of angle-closure glaucoma for all indications per routine pharmacovigilance.</td><td colspan="3">Not applicable</td><td></td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Adverse testicular effects of Botox® in mature rats

Summary (The summary reflects the authors' opinions and conclusions. Allergan's comment follows this summary.): Thirty-six male Wistar rats were randomly assigned to 4 groups of 9 rats each. The rats were treated with either saline (0.9%) control or BOTOX at 10, 20 or 40 U/kg via intracremasteric injection at two-week intervals (week 1, week 3, and week 5). The animals were sacrificed 2 weeks after the third (last) injection. Blood samples and body weights were collected prior to termination. At necropsy, testes were divided into groups of six testes each: six kept in 10% formalin for histopathological and immunohistochemical examinations, six homogenized (10% homogenate) in saline, and the last six stored as such in −80 °C for flowcytometric analysis. Sperm parameters were assessed in the epididymal suspension. Breikaa and colleagues observed BOTOX-related decreases in body weight, gonadosomatic index (a ratio of the testes to the body weight), and sperm quality, count, motility, morphology and viability. Histologic observations were consistent with testicular atrophy in rats treated with ≥ 10U/kg of BOTOX.</td><td rowspan="3">Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="5">Opinions of the company</td><td colspan="2">Future correspondence</td></tr>
<tr><td colspan="5">Allergan has seen similar findings in rodent studies given IM or intraprostatic BOTOX. Testicular and epididymal findings (degeneration, atrophy, and decreased organ weight) in rats given ≥ 20 U/kg intraprostatically were similar to that observed following single (or repeat) IM doses of BOTOX in this species (Reports 1658L-3008-16 and TX970647). Testicular degeneration reflected the short-term (≤ 2 weeks) findings and testicular atrophy characterized the longer-term (4 week) findings. There are several lines of evidence to suggest that these testicular effects are secondary to postural changes resulting from injection and not a direct effect of BOTOX. Rats have open inguinal canals, unlike humans or primates, which may lead to inguinal or abdominal retention (cryptorchidism) and testicular changes secondary to postural changes in the hind limb. Prevention of testicular and epididymal movement through the inguinal canals to the abdomen by surgical ligation of the inguinal canal prior to postural changes in rats prevents these testicular lesions.8 It is likely that this mechanism also explains the testicular lesions following IM injection in both the Allergan studies and the study published by Breikka and colleagues.</td><td colspan="2">Not applicable</td></tr>
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<tr><td>Brand name (manufacturer’s name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">The role of neurotoxins in the periorbital and midfacial areas

Initially popularized for the treatment of strabismus and blepharospasm, injection of botulinum neurotoxin has become the most commonly performed cosmetic treatment in the US. Injection techniques have been particularly well-studied in the midface and periocular region, and patient satisfaction tends to be very high. The articles reviews the salient differences among available neurotoxins, how to optimally reconstitute them, how to inject the forehead, glabella, lateral canthal lines ("crow's feet"), infralid region, and transverse nasal lines ("bunny lines"), how to sculpt the brow, and how to manage potential complications.</td><td rowspan="3">Remarks on ‘Precaution for use’ and references, etc.

4. Adverse Events
H. Glabellar lines
I. Crow’s Feet Lines
K. International Post-Marketing Experience

5. General precaution
I. Upper Facial Lines (Glabellar lines and Crow’s Feet Lines)

9. Geriatric use</td></tr>
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<tr><td colspan="5">This article explained that BOTOX COSMETIC injection in the intramuscular or subcutaneous, depending on injector preference, has equivalent efficacy in split face studies. For Asian patients, more conservative dosing with 1 unit per injection site may be warranted and many Asians rely on the frontalis muscle to act as a secondary brow elevator, so forehead injections should therefore be conservative.</td><td colspan="2">Not applicable</td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Botulinum toxin in masticatory muscles of the adult rat induces bone loss at the condyle and alveolar regions of the mandible associated with a bone proliferation at a muscle enthesis

In man, botulinum toxin type A (BTX) is injected in masticatory muscles for several indications such as trismus, bruxism, or masseter hypertrophy. Bone changes in the mandible following BTX injections in adult animal have therefore became a subject of interest. The aim of this study was to analyze condylar and alveolar bone changes following BTX unilateral injections in masseter and temporal muscles in adult rats. Mature male rats (n = 15) were randomized into 2 groups: control (CTRL; n = 6) and BTX group (n= 9). Rats from the BTX group were anesthetized with isoflurane and injected intramuscularly with 2U of type A BTX: 1 U in 0.2 mL in the Mus Masseter and 1 U (in 0.2 mL) in the Mus Temporalis (BOTOX, Allergan Inc., Irvine, CA, USA). Three points of injections for each Mus Masseter and 2 for each Mus Temporalis were necessary. Rats of the CTRL group were similarly injected with saline solution. Rats were sacrificed 4 weeks after injections. Masticatory muscles examination and microcomputed tomography (microCT) were performed. A significant difference of weight was found between the 2 groups at weeks 2, 3, and 4 ($p < 0.05$). Atrophy of the right masseter and temporal muscles was observed in all BTX rats. MicroCT analysis showed significant bone loss in the right alveolar and condylar areas in BTX rats. Decrease in bone volume reached -20% for right alveolar bone and -35% for right condylar bone. A hypertrophic bone metaplasia at the digastric muscle enthesis was found on every right hemimandible in the BTX group and none in the CTRL group. BTX injection in masticatory muscles leads to a significant and major mandible bone loss. These alterations can represent a risk factor for fractures in humans. The occurrence of a hypertrophic bone metaplasia at the Mus Digastricus enthesis may constitute an etiological factor for tori.</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="5">Opinions of the company</td><td colspan="2">Future correspondence</td><td rowspan="2"></td></tr>
<tr><td colspan="5">This article refers an off-label use of botulinum toxin injection in masseter and temporal muscles in adult rats to study bone changes in the mandible following the BOTOX injection. The study demonstrated that the bone loss was seen on the site of injection of alveolar bone in the BTX group. However, this remains to be studied in humans since there are many differences between rate and human masticatory functions (masticatory apparatus, bone volume dosage of BTX). Of note, Allergan is currently conducting an ongoing clinical study to evaluate the safety and efficacy of BOTOX for treatment of bilateral masseter muscle hypertrophy (a phase 2 randomized, double-blind, placebo-controlled study, 191622-130).</td><td colspan="2">Not applicable</td></tr>
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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="5">Effect of Botulinum Toxin Type A on Differentiation of Fibroblasts Derived from Scar Tissue

Summary: Scar tissue specimens from 10 scars (five normal mature scars and five hypertrophic scars) were obtained from nine patients who visited the authors' department for scar revision. Fibroblasts isolated from the tissue specimens were cultured until confluent and pretreated with TGF-β1 to induce differentiation before treatment with botulinum toxin type A. Expression of the myofibroblast marker α-smooth muscle actin in cell cultures was evaluated by enzyme-linked immunosorbent assay and quantitative reverse transcription polymerase chain reaction. Fibroblast-to-myofibroblast differentiation was further evaluated by immunocytochemistry and confocal microscopy. The results showed that α-smooth muscle actin mRNA and protein levels were significantly lower in the botulinum toxin type A–treated group than in the control group (treated with TGF-β1 only) of fibroblasts derived from hypertrophic scars, but not fibroblasts derived from normal scars. Immunocytochemistry results also showed that fibroblast-to-myofibroblast differentiation was significantly decreased after botulinum toxin type A treatment in fibroblasts derived from hypertrophic scars.</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="4">Opinions of the company</td><td colspan="2">Future correspondence</td><td></td></tr>
<tr><td colspan="4">The significance of this publication is that the authors have shown that botulinum toxin A directly inhibits fibroblast-to-myofibroblast differentiation in vitro, and indicate its potential for use in treating wounds expected to develop into hypertrophic scars after trauma, burn, or surgery. The clinical safety implication of this early pre-clinical research finding is still unknown.</td><td colspan="2">Not applicable</td><td></td></tr>
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General name	Clostridium Botulinum Toxin Type A		**Publication status of study reports**	Not applicable	**Publishing country**	
Brand name (manufacturer's name)	Botox Inj. 50 units (Allergan Korea Ltd.)					
Abstract	**Ultrasound-guided botulinum toxin type A salivary gland injection in children for refractory sialorrhea: 10-year experience at a large tertiary children's hospital** **Background:** Sialorrhea is problematic for neurologically-impaired children, and botulinum toxin A salivary gland injection has been reported as effective in reducing sialorrhea. This article assesses the success and safety of ultrasound-guided weight-based botulinum toxin A injection for the management of sialorrhea in children. **Methods:** A total of 111 patients (63 males, 48 females; average age 7 years) with refractory sialorrhea were treated with ultrasound-guided botulinum toxin type A salivary gland injections (144 procedures) from 01-July-2004 to 01-July-2014, using a single weight-based protocol. Patient history, procedural records, and clinical follow-up documents were retrospectively reviewed. Clinical data were compared with reported effectiveness and complications using odds ratios. **Results**: A total of 144 procedures were performed in 111 patients with refractory sialorrhea. Cerebral palsy was the most common underlying etiology for sialorrhea (29%), whereas others included encephalopathy (5%), anoxic brain injury (4%), and a variety of chromosomal anomalies (5%). There was a 100% technical success rate. Overall treatment effectiveness was 68%. Repeat injections were not associated with increased clinical success. No procedure-related deaths or major complications were identified; the minor complication rate was less than 2%. **Conclusions:** The protocol used for ultrasound-guided injection of botulinum toxin A proved to be safe and effective in children suffering from sialorrhea. Image guidance technique may lead to a reduction in rates of AEs reported in other series. Subsequent procedures do not improve upon initial efficacy.					**Remarks on 'Precaution for use' and references, etc.** 1. Warnings I. Injection in or near vulnerable anatomic structures
Opinions of the company				**Future correspondence**		
The authors noted that the use of ultrasound for the unapproved indications of refractory sialorrhea likely decreased the number of potential complications, particularly in patients less than 10 kg, because the complication rates were lower than many reported series that did not employ image guidance.				Not applicable		

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<tr><td>Brand name (manufacturer's name)</td><td colspan="2">Botox Inj. 50 units (Allergan Korea Ltd.)</td></tr>
<tr><td>Abstract</td><td colspan="6">Influence of onabotulinumtoxin A on testes of the growing rat

Adverse testicular effects of Botox in mature rats

Twenty-four immature male Wistar rats were randomly assigned to 4 groups of 6 rats each. The rats were one month old (~30 days) at study start, and study duration was 6 weeks, so rats were ~70 days old at necropsy. Rats were injected bilaterally in the cremaster muscles with either saline (0.9% = control) or BOTOX at 10, 20 or 40 U/kg every 2 weeks for 3 total injections. The animals were sacrificed 2 weeks after the third (last) injection. Serum samples were collected prior to termination. At necropsy, testes were collected. The authors describe that "part of the testes was kept in 10% formalin, part homogenized in saline, and part stored as such in -80°C for flow cytometric analysis". (MAH comment: This was not clear. Based on study methods described in the 2014 paper by the same authors, this likely meant that of the 12 testicles per group [6 animals/group], 4 were taken for each of the 3 analyses. It was not addressed if these came from the same or separate animals). Sperm parameters and semen quality were assessed from a suspension from the cauda epididymis. The following parameters were evaluated: Sperm parameters including sperm counts, motility, vitality, and morphology; semen quality via resazurin reduction; serum testosterone and antisperm antibodies; immunohistochemistry for Fas, Bax, and Caspase 3 as markers for apoptosis; histology; and DNA flow cytometry for haploid versus diploid germ cells.

Breikaa et al reported that in rats given ≥ 10 U/kg, there were decreases in sperm count and sperm motility (without effect on sperm vitality and sperm morphology); decreases in semen quality; and an increase in Fas, Cas3, and Bax immunohistochemical (IHC) staining as markers of apoptosis.

Breikaa et al reported that in rats given ≥ 20 U/kg, there were increases in antisperm antibodies; a decrease in the proportion of haploid cells via DNA flow cytometry; and histologic alterations of increased apoptosis and necrosis, and changes consistent with testicular atrophy.

Parameters that were unaffected were the following: serum testosterone, sperm vitality, and sperm morphology.</td><td>Remarks on 'Precaution for use' and references, etc.
Not applicable</td></tr>
<tr><td colspan="5">Opinions of the company</td><td colspan="2">Future correspondence</td></tr>
<tr><td colspan="5">Allergan has seen similar findings in rodent studies given IM or intraprostatic BOTOX. Testicular and epididymal findings (degeneration, atrophy, and decreased organ weight) in rats given ≥ 20 U/kg intraprostatically were similar to that observed following single (or repeat) IM doses of BOTOX in this species (Allergan internal reports 1658L-3008-1 and TX97064). Testicular degeneration reflected the short-term (≤ 2 weeks) findings and testicular atrophy characterized the longer-term (4 week) findings. There are several lines of evidence to suggest that these testicular effects are secondary</td><td colspan="2">Not applicable</td></tr>
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to postural changes resulting from injection and not a direct effect of BOTOX. Rats have open inguinal canals, unlike humans or primates, which may lead to inguinal or abdominal retention (cryptorchidism) and testicular changes secondary to postural changes in the hind limb (Tash et al, 2002). Cryptorchidism (testicles retained in the abdomen) is known to cause testicular germ cell apoptosis, and induced cryptorchidism is exploited to create a model to study testicular germ cell degeneration and apoptosis (Kwon et al, 2004). Prevention of testicular and epididymal movement through the inguinal canals to the abdomen by surgical ligation of the inguinal canal prior to postural changes in rats prevents these testicular lesions (Tash et al, 2002). It is likely that this mechanism also explains the testicular lesions in rats following IM injection in the Allergan studies and is at least partially responsible for the results presented in the studies in rats published by Breikka et al. *However, it is impossible to completely evaluate the results presented by Breikaa et al 2016, as multiple parameters important for evaluation of study results were not addressed by the authors in the paper. Additionally, many of the methods used did not support the results as interpreted and/or depicted by the authors.* *Parameters important for evaluation of study results that were not addressed by the authors included clinical condition of the animals including any observations of muscle paresis or paralysis after injections; body weights; testicular weights; food consumption; dose volume; and terminal dexoynucleotidyl transferase dUTP nick end labeling (TUNEL) staining for apoptosis. In addition to the effects of postural changes on testes, decreases in body weight and decreases in food consumption can delay sexual maturation (Creasy, 2012*). A delay in sexual maturation would produce the altered parameters described in report. Especially with immature rats, testicular weight changes are important for evaluation of the progression of maturity and testicular toxicity. Dose volume would be important to compare to the volume of the cremasteric muscles, as exceeding the volume of these muscles would likely lead to diffusion of the toxin into the surrounding and adjacent tissues, as well as systemic spread of toxin, which would then lead *to decreased movement and postural changes as a consequence of toxin diffusion. TUNEL staining is the standard stain to demonstrate apoptosis, and was not reported by the authors.* *Clinical observations of the condition of the rats would allow the reader to evaluate whether or not the known systemic effects of onabotulinum toxin A such as muscle paresis/paralysis, or difficulty breathing were present. This is especially important in the context of this paper because paresis or postural changes in rats can produce testicular atrophy (Tash et al, 2002). Clinical observations were not provided by Breikka et al in either paper, but in the discussion of the 2014 paper the authors state that there was "severe muscular atrophy and bone degradation in the Botox-injected groups". Note that the only tissues reported to have been evaluated in either paper were testes and sperm. The severe weight loss reported by the authors in the 2014 paper (failure to gain in 10 U/kg group; 42% decrease in body weight in 20 U/kg group; >75% decrease in body weight in 40 U/kg group) strongly suggested the presence of muscle atrophy and muscle paresis/paralysis.* *Decreases in body weight and/or food consumption can delay sexual maturation in rats (Creasy, 2012) and many other*		

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species (Huchard, 2016). The authors did not publish the body weights in this 2016 article. Based on the doses administered, and comparison to results published by the same group in 2014, body weights were likely severely affected, and thus, likely led to significantly delayed maturity. (In the 2014 paper utilizing reportedly mature rats, Breikaa et al reported that the 10 U/kg group failed to gain weight and ended up with a 40% decrease in body weight compared to controls by study end, and the 20 and 40 U/kg groups lost ~42%, and 75% of their starting body weights, respectively, by study end.) Immature testes undergoing sexual maturation have increased apoptosis, increased multinucleated germ cells, and many changes that mimic testicular degeneration (Creasy, 2012), making it difficult to evaluate a toxic effect. When a test article negatively affects body weight in dosed groups, and thus the rate of sexual maturation, this can produce dose-related changes that are due to differences in sexual maturity. Thus, body weight-induced delay in sexual maturity likely contributed significantly to the changes described by Breikaa et al in this 2016 article. Additionally, since a body weight of 150 to 200 g in Wistar rats corresponds to an age of ~45 days according to Campion et al, and ~30 to 45 days according to the Charles River website, the Wistar rats studied by Breikaa et al in 2014 were also likely immature at study start. (A sexually mature Wistar rat at ~70 days should weigh at least ~300 g). Therefore body weight-induced delays in sexual maturation also likely significantly added to the findings noted in the 2014 article. *Injection dose volumes used by Breikka et al: Based on information provided within the 2014 article, 100 U BOTOX was reconstituted in 4 mL saline to a final dilution of 25 U/mL. Rats in the 2014 article weighed from 150 to 200 g at study start. In a 200 g rat, the dose range was therefore 2 to 8 U, with a corresponding dose volume of 200 to 320 µL. Body weights, method of reconstitution, and dosing volume were not reported in the 2016 article by Breikaa et al. Based on reports in the literature, 30 day old Sprague-Dawley rats should weigh ~100 to 150 g, and ~350 to 400 g at 70 days. If the same methods were used as reported in the 2014 article, the dose range for a 100 g rat would be 1 to 4 U, with a corresponding dose volume of 100 to 160 µL. In the mature laboratory rat, the cremaster muscle is approximately 250 microns in thickness and 2 to 3 cm in diameter (Majno and Palade, 1961; Grant, 1964; Baez, 1973). Using these dimensions, the estimated volume of the cremaster muscle in mature rats was calculated to be 78 to 177 µL. An immature rat would have a lesser volume. Since the injected volume exceeded the estimated volume capacity of the cremaster muscle, diffusion of the toxin into the surrounding and adjacent tissues, as well as systemic spread, were likely. While clinical observations were not provided by Breikka et al, decreased movement and postural changes as a consequence of toxin diffusion were also likely.* *Immunohistochemistry for apoptosis using staining for Fas, Bax, and Cas3 but not TUNEL: Staining depicted for all 3 markers was diffuse throughout the tissue including support structures such as the basement membrane, interstitium, and Sertoli cells. On a subcellular level, staining was diffuse throughout the cytoplasm and nucleus of all cells. Additionally, no negative controls were depicted to demonstrate specificity of the staining. IHC staining should be specific for the cell type being targeted, and often has subcellular localization that is specific. Diffuse staining*		

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implies nonspecific staining. To get quantitative data from IHC staining via image analysis, it is especially important that all staining is specific with adequate controls for intensity of staining. The nonspecific staining depicted in the article would not be valid for generating quantitative data using image analysis software. Additionally, markers used to demonstrate a process such as apoptosis should agree with what is known about the biology of the process, including timing and subcellular localization. TUNEL staining (Gavrieli, 1992) is the most common IHC staining used to demonstrate apoptosis, but this was not utilized in this article. Timing-wise, since these tissues were collected 2 weeks after the last injection, any changes present would be those expected 2 weeks after exposure. *Fas is widely expressed in tissues and is not specific for apoptosis. The interaction of Fas on the target cell with Fas ligand (FasL) on the effector cell is necessary to induce apoptosis, and therefore the demonstration of the interaction of Fas with FasL positive cells would be much more supportive of apoptosis induction than Fas staining alone. Kokkonen and Karrtunen, 2010 took great care to demonstrate the correlation between Fas, FasL, and TUNEL positive individual cells to demonstrate the correlation with apoptosis in their article. Lee et al, 1999 demonstrated that germ cell specific toxicity will induce upregulation of Fas in the testes. However, the interaction with FasL on Sertoli cells was necessary for apoptosis, and Lee et al used TUNEL staining to correlate their findings to apoptotic events. Additionally, the upregulation of Fas occurs ~12 hours after the toxic insult; not 2 weeks.* *Bax is also widely expressed in cells and not specific for apoptosis on its own. When apoptosis is induced, Bax will translocate from the cytosol to mitochondria producing a characteristic punctate IHC staining under conditions of apoptosis that occurs within 30 minutes of induction (Wolter, 1997). Therefore, the diffuse Bax staining depicted in the article, as well as the timing (2 weeks after exposure), do not provide support for the authors' conclusion of increased apoptosis based on the Bax staining depicted in their results.* *Caspase3 is one of several proteins involved in apoptosis but is subject to modification after upregulation and therefore its presence does not demonstrate apoptosis. Kwon et al 2004 looked at a model of cryptorchidism-induced germ cell apoptosis in mice, and included caspase3 in their assessments. Despite demonstrating significant apoptosis in some of the experimental groups, changes in caspase3 were described as minimal, and therefore not detailed in the Kwon 2004 article. As with other authors, the IHC method used by Kwon et al to demonstrate germ cell apoptosis was TUNEL staining. In this model, the changes in germ cell apoptosis were quantified by demonstrating differences in the percentage of seminiferous tubules containing apoptotic cells, and the average number of apoptotic cells/tubule. There were 3 categories of number of apoptotic cells/tubule; 1 to 5, 6 to 10, and >11, showing that apoptosis should be confined to only a few cells/tubule at any given time. This also was not consistent with the diffuse staining depicted by Breikaa et al 2016 and interpreted to be demonstrating increased apoptosis.* *Since testicular changes have not been observed in monkeys following IM (Allergan internal reports 91-3708, 94-324,1 and TX99009) or intraprostatic BOTOX injection (Allergan internal reports TX01063, TX02012, TX05055, and TX07077)*		

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and no effects on human spermatogenesis have been observed following IM BOTOX injection, these findings in rats are considered species specific, and, therefore, are not relevant for human risk assessment of botulinum toxin type A injection. Additionally, the testicular degeneration in Sprague-Dawley and Wistar rats described by Breikaa et al (in 2016 and 2014) were likely due to systemic spread of BOTOX following injections, with resultant paresis/paralysis, and secondary effects on testicles due to postural changes, poor clinical condition, with contribution from delays in sexual maturation during the course of the studies.		

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[Appendix 10] Oversea Manufacturing Suspension, Recall, and Disposal Report

Not applicable