VI.2 Elements for a Public Summary for BOTOX®

VI.2.1 Overview of disease epidemiology for BOTOX®

9.1 Blepharospasm (Muscle Spasms of the Eyelids)

Blepharospasm (which is involuntary and uncontrollable blinking) is a disorder of the muscles of the eyelid. It affects about 2 to 4 persons out of every 100,000 people, mainly middle aged to older adults, and women more frequently than men. Blepharospasm can be caused by dysfunction of the nerves of the eyelid, or it can run in families whose members have movement disorders (conditions in which there is a loss of control over one or more parts of the body). People at risk for developing blepharospasm include those who have had head/face trauma, other diseases of the eyelid, or diseases of the surface of the eye (the cornea). If the cause of the blepharospasm cannot be diagnosed, the condition is called 'benign essential blepharospasm' or 'BEB'. The first noticeable symptom of blepharospasm is an increased frequency of blinking, particularly in response to a variety of common triggers, including wind, air pollution, sunlight, noise, movements of the head or eyes, or stress. Other possible symptoms include sensitivity to light, irritation of the cornea of the eye, and dry eye. These symptoms progress to the point where the eyelid blinks almost all the time and can't be stopped. At first only one eye is affected, but eventually both eyes can be affected. If it is not treated, blepharospasm can result in eye pain and significantly reduced vision.

9.2 Hemifacial Spasm (Muscle Spasms of the Face)

Hemifacial spasm (HFS) is a disorder in which the muscles on one side of the face contract (or 'spasm' or 'twitch') uncontrollably and almost all of the time. It affects about 10 to 11 persons out of every 100,000 people, most frequently middle aged to older females. The causes of HFS include injury to the nerves and/or blood vessels of the face, tumours of the face, or stroke, or the cause may be unknown. The first symptom of HFS is usually twitching of the eyelid every now and then, but the twitching can get worse and more frequent and eventually force the eyelids to close completely. The spasms may then gradually spread to the muscles of the lower face and cause the mouth to be pulled to one side. Eventually, the spasms involve all of the muscles on one side of the face; the spasms are usually uncontrollable and are present almost all of the time. Hemifacial spasm can significantly affect a patient's quality of life.

9.3 Strabismus (Crossed Eyes)

Strabismus (or 'crossed eyes') is a disorder of the eye muscles that usually develops during childhood but which can occur at any age. Premature infants and infants who don't weigh enough at birth are examples of the types of children who have a risk of developing strabismus. In this disorder, there is a lack of coordination between the eyes because of dysfunction of the nerves that control the eye muscles. Usually one eye points straight ahead while the other eye points either inward, outward, up, or down. As a result, the eyes look in different directions and do not focus at the same time on a single point. Strabismus affects about 40 persons out of every 1,000 people, and of those affected, about 3 out of every 1,000 require treatment. If strabismus is not treated it can result in major vision problems. It is the most common cause of amblyopia (or 'lazy eye'), in which vision is reduced but cannot be helped with glasses or contact lenses.

9.4 Cervical Dystonia (Muscle Spasms of the Neck and Shoulder)

Cervical dystonia (or 'CD') is a disorder of the neck muscles that causes involuntary and uncontrollable movements of the neck (such as twisting). It affects about 6 to 9 persons out of every 100,000 people, and mainly women. It can run in families, or it can be diagnosed in a patient with no family members who have ever had the disorder. In most cases, the cause of the CD is unknown. The first noticeable sign of CD is often spasms of the neck that force the head to move forward, backward, sideways, or to twist to the left or right. The neck spasms may be constant or sporadic, and are often painful. The neck spasms and abnormal head movements can also prevent the patient from performing routine daily activities. The disease worsens very gradually, usually over the first 5 years, and then the symptoms level off. If CD is not treated, it can begin to affect the spine in the neck area which can lead to compression (or 'pinching') of the nerves that come from the spinal cord. Studies have also shown that CD can lead to psychological/emotional distress, including mental disorders such as depression.

9.5 Focal Spasticity (Muscle Spasms of the Arm and Leg) in Children with Cerebral Palsy

Cerebral palsy (CP) (which can also be called Juvenile Cerebral Palsy, or 'JCP') is a disease that appears in infancy or early childhood that causes physical disability by permanently affecting body movement and muscle coordination, but it doesn't worsen over time. In addition to abnormal/spastic movements, other health problems in children with CP include respiratory illness (such as pneumonia), mental retardation, seizures, delayed growth and development, and deformities of the spine. Cerebral palsy affects 23 persons (17 years of age or younger) out of every 10,000 people, mainly males. There are multiple causes of CP, and these usually occur

during pregnancy before the infant is born. However, CP can also occur after birth in the first few months or years of life, due to brain damage from brain infections (such as bacterial meningitis or viral encephalitis), head injury, or child abuse. Children with milder forms of CP can have a life-span similar to healthy children. However, the life-span of children who are severely affected is greatly reduced. All CP patients have problems with body movement to some degree, and about 70% to 90% of all CP patients have muscle spasms. About 60% of all CP patients have dynamic equinus gait (or 'club foot'), which is the specific condition that BOTOX® is approved to treat.

9.6 Upper Limb Spasticity (Muscle Spasms of the Wrist and Hand) and Lower Limb Spasticity (Muscle Spasms in the Ankle) Associated with Stroke in Adult Patients

'Spasticity' or 'spasm' (which is the constant and uncontrollable movement of muscles) of the upper and lower limbs may occur after a stroke because the stroke has damaged the part of the brain that controls the limbs. This condition is most frequently seen in elderly patients of either sex. Immediately after a stroke, the most common symptom is paralysis (no muscle tone at all). The muscle spasms often do not develop until weeks, months, or even years after a stroke. At 12 months after a stroke, about 17% to 19% of stroke survivors were found to have spasms of the upper limb and about 11% to 32% were found to have spasms of the lower limb. The uncontrollable and unwanted muscle spasms can significantly impact the stroke survivor's quality of life. The patients' spastic movements can affect their routine daily physical activities such as walking, washing, and dressing. Spasticity after stroke has also been found to be associated with pain in approximately 11% to 65% of patients. It is possible that the risk of developing post-stroke muscle spasms is increased in patients who start to have arm and leg weakness and difficulty with activities of daily living very soon after the stroke occurs; in patients whose problems after the stroke are primarily on the left side of the body rather than right side; and in patients with a history of smoking.

9.7 Hyperhidrosis (Excessive Sweating) of the Armpits

Hyperhidrosis (HH) is excessive sweating, and it can occur under the armpits, or in the hands, feet, or face. The cause of hyperhidrosis is often unknown (this is called 'primary' hyperhidrosis), or it can be due to an underlying condition such as infection, gland disorders, or disorders of metabolism, etc. (this is called 'secondary' hyperhidrosis). Hyperhidrosis affects about 1% to 3% of the general population, mainly young adults to middle aged patients. A very severe case of hyperhidrosis can affect a patient's quality of life.

9.8 Neurogenic Detrusor Overactivity (Bladder Problems) Associated with Spinal Cord Injury or Multiple Sclerosis

'Neurogenic bladder' is a disorder which affects the bladder muscle that contracts to push urine out of the bladder (the ‘detrusor’ muscle). In this disorder, the bladder muscle can either be underactive or overactive (the most common form). In the underactive form, the detrusor muscle is less able to push urine out of the bladder, so the patient is unable to urinate and urine stays in the bladder. In the most common form, which is called 'neurogenic detrusor overactivity' (or 'NDO'), the detrusor muscle cannot be controlled, and this leads to the involuntary release of urine, often at inappropriate times (‘urinary incontinence’). About 10% of patients with urinary incontinence have NDO, and most of them are older women. Although oral drug treatments are available, they often do not work or have side effects that cannot be tolerated. The underlying diseases that can cause a patient to have NDO include multiple sclerosis (MS), spinal cord injuries that lead to partial or total paralysis, Parkinson’s disease, stroke, cerebral palsy, and spina bifida. Neurogenic detrusor overactivity can significantly affect a patient's quality of life and also lead to more serious problems if it is not treated. Over one year, 29% of NDO patients had urinary tract infections, 14% had urinary retention, 8% had blood in the urine, 2% had serious kidney infections, 2% had vaginal infections, and 1% had bladder stones. It is also possible that untreated NDO can lead to death from a serious urinary tract infection that causes the kidneys to shut down.

9.9 Overactive Bladder

Overactive bladder (OAB) is a disorder in which a patient has an increased urge to pass urine, with or without the involuntary release of urine ('urinary incontinence'). Usually the patient has to urinate more frequently during the day, and also is awakened from sleeping at night by the need to urinate. About 3% to 6% of adults with urinary incontinence have incontinence due to OAB. The disorder usually affects older adults, and about twice as many females than males. Although oral drug treatments are available, they often do not work or have side effects that cannot be tolerated. Studies have shown that OAB can be linked with certain factors, such as age, gender, body weight, and certain diseases (such as diabetes, deep vein thrombosis, osteoporosis, bowel urgency, prostate problems, psychological problems, or sexual impairment). If OAB is not treated, it can significantly affect a patient's quality of life and also lead to more serious problems such as urinary tract infections, skin ulceration from urine leakage, and falls and fractures (especially in the elderly).

9.10 Chronic Migraine

Migraine is a disorder in which a patient has recurring headaches. It is called 'episodic migraine' if the patient experiences headache less than 15 days per month. It is called 'chronic migraine' if the patient experiences headache on 15 or more days each month of which at least 8 days are with migraine. Chronic migraine type of headaches are moderate to severe headaches typically located in one area of the head. The patient may feel as if the head is 'pulsating'. The headache may be caused by routine physical activity, such as walking or climbing stairs, or the patient may avoid such activities because of the fear of triggering the headache. When the headache is present, the patient may also have nausea, vomiting, and/or sensitivity to light and/or sound. Chronic migraine affects about 1% to 2% of the general population, mainly middle aged Caucasian females. If chronic migraine is not prevented or is left untreated, it can be quite painful and can significantly affect a patient's quality of life.

9.11 Glabellar Frown Lines (Vertical Lines between the Eyebrows seen at Frown) and Lateral Canthus Lines (Crow's Feet Lines)

One of the first places on the face to show signs of aging is the area around the eye (the 'lateral canthus' area). It is estimated that 90-95% of Caucasian women and 25% of Asian women have noticeable lateral canthal lines (crow's feet lines) by the time they are 31-40 years old. Another early sign of ageing is glabellar frown lines, which are the ‘no. 11’ parallel lines between the eyebrows. It is estimated that 70% of Caucasian women and 20% of Asian women have noticeable glabellar frown lines by the time they are 31-40 years old. These two types of wrinkles most often occur together.

Ageing of the face results from the combined effects of 'atrophy' (wasting away of a part of the body) and a loss of fullness of the face, bone loss, decreased 'elasticity' (decreased ability of the skin to return to shape when stretched), and gravity. Ageing is also influenced by genetic factors, by environmental factors such as exposure to the sun or to the chemicals in cigarette smoke. With the skin loses elasticity, repeated facial expressions can become permanent lines. If the wrinkles are severe, they can affect the patient's quality of life.

VI.2.2 Summary of treatment benefits for BOTOX®

9.12 Blepharospasm (Muscle Spasms of the Eyelid)

In Study 191622-003, a total of 98 adult patients (35-79 years old) received BOTOX® injections into the muscles of both eyelids at an average dose of 33 Units per eyelid. Treatment success was measured on a scale of 0 to 4 where 0 was equal to ‘none’ and 4 was equal to ‘severe’ spasm of

the eyelid. About 90% of the patients had treatment success 4 weeks after receiving BOTOX®, and about 50% of the patients had treatment success 12 weeks after receiving BOTOX®.

9.13 Hemifacial Spasm (Muscle Spasms of the Face)

In Study BTOX-504-8051, a total of 56 patients (42-78 years old) received an average of 27 Units (dose range of 10-50 Units) of BOTOX® to the upper facial muscles. Patients who did not show any improvement after 4 weeks received another injection of BOTOX® (dose range of 5-50 Units). All 56 patients showed improvement, and 62.5% (35/56) showed exceptional improvement as defined in the protocol. When the upper facial muscles were evaluated, improvement was observed in all patients. When the lower facial muscles were evaluated, all but 2 patients showed improvement.

9.14 Strabismus (Crossed Eyes)

No clinical studies were conducted by Allergan. A literature article describes 9 years of use of botulinum toxin (the main ingredient in BOTOX®) in 677 patients (12-90 years old) with crossed eyes who received one or more injections (Scott, 1989). A total of 56% of the patients showed improvement when evaluated at 6 months or more (average 17 months) after treatment with BOTOX®.

9.15 Cervical Dystonia (Muscle Spasms of the Neck and Shoulder)

In Study BTX-140-8051, a total of 214 adult patients (29-77 years old) with cervical dystonia received an injection of BOTOX® to certain muscles of the neck and shoulder as determined by their doctors. The dose range for BOTOX® was 95-360 Units. At 6 weeks after treatment, significant improvement with BOTOX® compared to placebo was seen in head position, disease symptoms, the intensity and frequency of pain, and the ability to function.

In Study 191622-503, 135 adult patients (25-80 years old) with cervical dystonia and prior successful treatment with BOTOX® received two injections of 100-300 Units of BOTOX® to certain muscles of the neck and shoulder as determined by their doctors. The two injections were given 8-16 weeks apart. At 6 weeks after treatment, 35% of patients showed improvement in the severity of their symptoms and patients reported that pain decreased by an average of 50% from the start of the study. In addition, 85% of physicians and 80% of patients reported treatment success.

9.16 Focal Spasticity (Muscle Spasms of the Arm and Leg) in Children with Cerebral Palsy

Arm spasm: In two studies (BTOX-9060-708, BTOX-9060-715), treatment with BOTOX® plus standard care was compared to treatment with standard care alone for 6-months in 72 children (2-15 years old) with cerebral palsy and upper limb spasticity. BOTOX® was injected with an average dose of 137-153 Units into the muscles of the arm and hand. 'Standard care' consisted of a combination of occupational therapy, casts, and splints. In Study BTOX-9060-708, after 1 and 3 months, muscle spasms were significantly reduced and the quality of upper limb movement and improvement in function were better in children who received BOTOX® plus standard care, compared to standard care alone. In Study BTOX-9060-715, at month 3, the BOTOX®-treated children had a 14% improvement in upper limb function compared with no change in the group of children who received standard care alone.

Leg spasm: In two studies (OCUL-118-8051, OCUL-119-8051), treatment with BOTOX® was compared with placebo or no treatment for up to 42 months in about 200 children (2-16 years old) with cerebral palsy and equinus ankle position ('club foot') who were able to walk. BOTOX® was injected with up to 200 Units into the muscles of the leg no more often than every 30 days. In OCUL-118-8051, the doctors rated BOTOX® (given to 72 patients) as significantly more effective than placebo (66 patients) or no treatment (7 patients) in improving the patient's manner of walking ('gait'). Patients treated with BOTOX® (53-60%) reported improvement in their walking compared to patients who received placebo/no treatment (25-32%). BOTOX®-treated patients had improvements in their manner of walking and the position of their ankles while walking. In OCUL-119-8051, 41-67% of a total of 207 patientshad improvement in walking (as rated by the doctors). Individually, significant improvements were seen at every visit over the 3-year period.

9.17 Upper Limb Spasticity (Muscle Spasms of the Wrist and Hand) Associated with Stroke in Adult Patients

In a 12-week study (Study 191622-008), patients received one treatment with BOTOX® (64 patients) or placebo (62 patients) into the wrist, fingers and/or thumb muscles. There were 111 patients who also continued onto another long-term study (Study 191622-025) and received up to 3 treatments of BOTOX®. In both studies, 200-240 Units of BOTOX® was injected. In the 12-week study, at all study visits, wrist and finger movement was significantly better in BOTOX®-treated patients compared to placebo. Significant improvement in thumb movement was seen at all visits except one. In the long-term continuation study, improvements in wrist movement were maintained after BOTOX® treatments.

In Study BTOX-133/134-8051, patients received one treatment with BOTOX® at a dose of 360 Units (21 patients), 180 Units (23 patients) or 90 Units (21 patients), or placebo (26 patients) into the elbow, wrist, and fingers. All BOTOX® doses produced improvements in wrist and elbow movement, particularly wrist movement in the group receiving 360 Units. Improvement in finger movement was best in the groups receiving 180 Units and 360 Units.

Integrated data from 8 different studies in a total of 501 patients were analyzed. In this combined ('meta') analysis, there were greater improvements in elbow and finger movement in BOTOX®-treated patients compared to placebo.

9.18 Lower Limb Spasticity (Muscle Spasms of the Ankle) Associated with Stroke in Adult Patients

In a 48-week study (BTX108512), 300 U (58 patients) of BOTOX® or placebo (62 patients) were injected into different calf muscles, followed up by 3 injections with 300 U of BOTOX®. Patients receiving BOTOX® showed a significant greater reduction in ankle muscle tone (improvement) compared to placebo at weeks 4, 6 and 8. In a 52-week study (AGN/HO/SPA/001-191622 [BEST]), 274 patients received up to 2 treatments of either BOTOX® (139 patients) or placebo (135 patients) followed by up to 4 treatments of BOTOX®. The dose was tailored for each patient. When analyzing the group of patients who received treatments in their 3 calf muscles, the principal active functional goal achievement as assessed by the physician was significantly higher in the BOTOX® group as compared to placebo 10 weeks after the second injection (or 24 weeks if no second injection was given). In a 28-week study (BTOX-702-8051), 85 patients received 1 treatment of either BOTOX® 200 U (28 patients), BOTOX® 300 U (28 patients) or placebo (29 patients) into their calf muscles, followed by 1 treatment of BOTOX® 200U or 300 U in the same muscles. Patients receiving 300 U of BOTOX® showed a significant greater reduction in ankle muscle tone (improvement) compared to placebo 8 weeks after treatment. Patients receiving 200 U of BOTOX® did not show a significant improvement in muscle tone compared to placebo.

Across 8 clinical studies, BOTOX® was well tolerated in a total of 625 patients who received BOTOX® treatment in their calf muscles at an average dose of 295.5 U (range 25-800 U).

9.19 Hyperhidrosis (Excessive Sweating) of the Armpits

In a 16-week Study 191622-505, 93.8% (242 patients) receiving 50 Units of BOTOX® into the skin of each armpit (100 Units total) and 35.9% (78 patients) receiving placebo had at least a 50% reduction in sweating at 4 weeks after treatment. In a 12-month study 191622-506, 207 patients from Study 191622-505 continued to receive up to three BOTOX® treatments and

improved 4 weeks after first treatment (91.8% of patients) and second treatment (88.2%). Average time between first and second treatments was 23 weeks. About 32% of patients who received BOTOX® in both studies did not require any further BOTOX® to manage their excessive armpit sweating.

In study 191622-016, patients received either 100 Units (104 patients) or 150 Units (110 patients) of BOTOX®, or placebo (108 patients) up to 6 times for up to 1 year. Response was significantly greater in patient receiving 100 Units (54.8%) and 150 Units (49.1%) of BOTOX® compared to placebo (5.6%).

In study 191622-075, 144 adolescent patients (12-17 years) received 100 Units of BOTOX® up to 6 times for up to 1 year. Response to BOTOX® (54.9%) was similar to results in adults. Duration of effect also suggested that patients may need only 2-3 treatments of BOTOX® per year. These adolescent patients also had improvements in quality of life and reductions in social, physical, and emotional problems resulting from their excessive sweating.

9.20 Neurogenic Detrusor Overactivity (Bladder Problems) Associated with Spinal Cord Injury or Multiple Sclerosis

Two studies (191622-515 and 191622-516) were conducted in patients with spinal cord injuries or multiple sclerosis (MS) who either could not control the release of urine (‘urinary incontinence’) or who had to routinely catheterize to release urine, and who could not adequately manage their symptoms with approved oral drug treatments. These patients were treated with BOTOX® 200 Units (227 patients), BOTOX® 300 Units (223 patients), or placebo (241 patients), and they were followed up for 12 weeks. BOTOX® or placebo was injected into the bladder muscles with a needle and syringe. At 2, 6, and 12 weeks after treatment, patients in the BOTOX® groups had fewer episodes of the involuntary release of urine compared to the patients who received placebo. Patients who received BOTOX® also had greater improvements than placebo patients in specific bladder measurements and quality of life scores from a specially-designed questionnaire for patients with urinary incontinence.

9.21 Overactive Bladder

Two studies (191622-095 and 191622-520) were conducted in patients with symptoms of overactive bladder (OAB) who still had symptoms of OAB or experienced side effects after taking an anticholinergic medicine. The patients were treated with either 100 Units of BOTOX® (557 patients) or placebo (548 patients) injected into the bladder detrusor muscle, and they were followed up for 12 weeks. After 12 weeks, patients could request additional treatment, and after week 12 all patients (including those who had previously received placebo) were treated with

100 U of BOTOX®. At 12 weeks after treatment, patients who received BOTOX®, compared to patients who received placebo, had greater reductions in daily episodes of leaking urine (51% reduction in episodes in BOTOX® patients vs. 15% in placebo patients), going to the bathroom to urinate (18% vs. 1%), urgent urination (36% vs. 9%), and leaking urine during sleep (23% vs. 4%). The BOTOX® patients also had a greater improvement in the ability of the bladder to store urine compared to the placebo patients.

9.22 Glabellar Lines (Vertical Lines Between the Eyebrows) and Lateral Canthal Lines (Crow's Feet Lines or Fan-Shaped Lines From the Corner of the Eyes)

Glabellar Lines (Vertical Lines Between the Eyebrows): In two studies (191622-010, 191622-023), patients with moderate to severe glabellar lines were treated with either 20 Units of BOTOX® (405 patients) or placebo (132 patients). The doctors who conducted these studies judged that the severity of glabellar lines was significantly reduced for up to 120 days in the BOTOX® group compared to the placebo group, and that 80% of BOTOX®-treated patients had responded to the treatment at 30 days after injection compared to 3% of placebo-treated patients. Also, at 30 days after treatment, 89% of BOTOX®-treated patients felt that they had moderate or better improvement of their wrinkles, compared to 7% of placebo-treated patients. After completing these studies, patients were able to enter the long-term continuation Study 191622-018 and receive repeat BOTOX® treatments at 120-day intervals. (The patients who received placebo in the first two studies were switched to BOTOX® for the long-term continuation study.)

Lateral Canthal Lines (Crow's Feet Lines or Fan-Shaped Lines From the Corner of the Eyes): In two studies (191622-098, 191622-099), patients with moderate to severe crow's feet lines (CFL) were treated with either 24 Units of BOTOX® (528 patients) or placebo (529 patients). In Study 191622-099, an additional 305 patients were also treated with 44 U BOTOX® for the combined treatment of CFL and glabellar lines. After receiving 2 treatments and completing Study 191622-099, patients were able to enter the long-term continuation Study 191622-104 (The patients who received placebo in the first study were switched to BOTOX® or placebo for the long-term continuation study.). There was a statistically significant difference in the proportion of patients achieving a CFL severity rating of none or mild at maximum smile when measured by the physician and patient, favoring BOTOX® compared to placebo.

9.23 Chronic Migraine Prevention (Prophylaxis)

In two 56-week studies (191622-079, 191622-080), a total of 1,384 adults were treated with either 155 Units to 195 Units of BOTOX® or a placebo at two treatment sessions 12 weeks apart. They could then receive 3 additional treatments of BOTOX® for a maximum of 5 injections. (Patients who received placebo for the first two treatments were switched to BOTOX® for the

remaining three treatments.) Patients were allowed to use headache treatments (such as aspirin or acetaminophen) if they experienced a sudden headache. Patients who received BOTOX® treatment had a 50% reduction in headache days, the average number of moderate/severe headache days, and the total number of hours of headache on headache days. Results of headache tests and quality of life questionnaires showed that BOTOX® had a long duration of effect, and improved patient function, vitality, psychological distress, and overall quality of life.

VI.2.3 Unknowns relating to treatment benefits for BOTOX®

Not applicable

VI.2.4 Summary of safety concerns for BOTOX®

Table 9–51 Important Identified Risks for BOTOX®

Risk	What is known	Preventability
All Indications		
Allergic reactions (Hypersensitivity reactions)	Allergic reactions have been rarely reported. Symptoms usually occur with a short time after injection, and can range from mild reactions such as hives to more serious reactions such as swelling of the face or throat, wheezing, feeling faint, shortness of breath, or severe skin problems. In some cases the more severe reactions can be life-threatening. There has been one report of death from 'anaphylaxis' (an extreme allergic reaction); it is unknown if this patient had the reaction to BOTOX®, lidocaine, or some other drug.	Yes. The doctor's prescribing information for BOTOX® states that it should not be used in patients allergic (hypersensitive) to botulinum toxin type A or the inactive ingredients of BOTOX® (human albumin and sodium chloride). Also, it is generally recognized that patients who have a history of asthma, hives, or allergies to other medications are at greater risk of having allergic reactions to medicines.
Patients who suffer from diseases of the nervous system that affect the muscles, such as myasthenia gravis (MG), Lambert-Eaton syndrome, amyotrophic lateral sclerosis (Lou Gehrig's disease), or motor neuropathy (in which the muscles don't work correctly because of nerve problems) (Pre-existing neuromuscular disorders)	There have been a small number of reports in the medical literature that patients with pre-existing neuromuscular disorders may have more severe side effects, especially difficulty in swallowing (dysphagia) and problems breathing.	Yes. The doctor's prescribing information for BOTOX® warns of the possibility of more severe side effects in patients with pre-existing neuromuscular disorders, and recommends extreme caution when using BOTOX® in these patients. It is possible that the risk of severe side effects can be reduced by using the lowest dose possible, and, in some cases, by more accurately injecting the muscles by using a medical instrument called an 'electromyograph' that helps to guide the injections.
Becoming resistant to the	If BOTOX® is given too often or	Yes. The doctor's prescribing

Risk	What is known	Preventability
beneficial effects of BOTOX® (Immunogenicity, drug resistance and antibody formation)	the dose is too high, the body can produce substances called 'antibodies' which can reduce the beneficial effects of BOTOX®. However, it is still possible to have side effects even though the beneficial effects are reduced.	information for BOTOX® recommends that doctors use the lowest doses possible as infrequently as possible.
Spread of BOTOX® far away from the site of injection (Distant spread of toxin)	Side effects in areas of the body far away from the site(s) of injection have been reported very rarely and include reactions such as muscle weakness, constipation, being unable to urinate, difficulty in swallowing, and food or drink accidentally going into the lungs (via the windpipe) instead of the stomach, which in some cases may lead to pneumonia. Patients are at a greater risk of this side effect if they are treated with higher than recommended doses.	Yes. The doctor's prescribing information for BOTOX® recommends that doctors use the lowest doses possible, and, in some cases, suggests the use of a medical instrument called an 'electromyograph' that helps to guide the injections so that they can be made more accurately.
Neurology (or Nervous system disorders) Indications		
Difficulty swallowing (dysphagia) in patients treated for cervical dystonia (abnormal movements of the neck/head) or chronic migraine (Dysphagia in cervical dystonia and chronic migraine patients)	Difficulty swallowing (dysphagia) is a very common side effect in patients who receive injections in the muscles of the shoulder and neck. It can cause the patient to refuse to eat or drink, and in some cases the patient has to be fed through a tube until it resolves. It can also lead to more severe conditions such as pneumonia from food or drink going into the lungs (via the windpipe) rather than the stomach. Patients with a greater risk of dysphagia are those who already have a disease that can cause dysphagia, patients with smaller neck muscles, patients who receive injections on both sides of the neck, and patients who receive higher than recommended doses.	Yes. The doctor's prescribing information for BOTOX® recommends that doctors use the lowest doses possible and reminds them of the established recommended maximum doses.
Worsening of migraine/headache in patients treated for chronic migraine (Worsening or intractable migraine/headache in chronic migraine treatment)	Moderate to severe headaches and migraines are common side effects of treatment for chronic migraine. Periodic headaches and migraines are also part of the natural course of chronic migraine. They can also occur if patients overuse over-the-counter pain relievers.	No.
Urinary Bladder Disorder Indications		

Risk	What is known	Preventability
Urinary tract infection (UTI) in patients who receive injections in the bladder wall to stop the involuntary leakage of urine ('urinary incontinence') due to an overactive or 'neurogenic' bladder ('neurogenic' means due to a nervous system disease or disorder such as myasthenia gravis or spinal cord injury) (Urinary tract infection in patients with bladder disorders with urinary incontinence)	In clinical trials that studied BOTOX® for the treatment of urinary incontinence, more BOTOX® patients than placebo patients had UTIs. Mild to moderate UTIs (mainly bladder infections) were more common than severe UTIs (infections of the kidney). Patients who had inability to empty the bladder ('urinary retention') and had to use a catheter to empty the bladder were more prone to develop UTIs.	Yes. The doctor's prescribing information recommends that patients should not be treated with BOTOX® if they have a UTI at time of treatment. It also states that patients should receive antibiotics for 1-3 days before treatment, on the day of treatment, and for 1-3 days after treatment.
Inability to empty the bladder ('urinary retention') in patients who receive injections in the bladder wall to stop the involuntary leakage of urine ('urinary incontinence') due to an overactive or 'neurogenic' bladder ('neurogenic' means due to a nervous system disease or disorder such as multiple sclerosis or spinal cord injury) (Urinary retention in patients with bladder disorders with urinary incontinence)	In clinical trials that studied BOTOX® for the treatment of urinary incontinence, more BOTOX® patients than placebo patients had urinary retention. Mild to moderate urinary retention was more common than severe urinary retention. A common treatment is for the patient to use a catheter to empty the bladder. Patients who are unable to completely empty the bladder naturally, and especially those who first start catheterizing the bladder to empty it, are prone to develop urinary tract infections (UTIs, primarily bladder infections).	Yes. The doctor's prescribing information recommends that patients should not be treated with BOTOX® if they are retaining urine but not routinely using a catheter to empty the bladder. If BOTOX® is used to treat urinary incontinence in patients who are not using a catheter to empty the bladder, it is recommended that the patient periodically visit the doctor (starting at 2 weeks after treatment and up to 12 weeks after treatment) to have a measurement of the amount of urine retained in the bladder to determine if the patient needs to start/adjust catheterization.
Upper Facial Lines Indications		
Drooping of the eyelid following injections to the vertical lines between the eyebrows seen at maximum frown or to the fan-shaped lines from the corner of the eyes seen at maximum smile when treated alone or at the same time as vertical lines between the eyebrows seen at maximum frown (Eyelid ptosis in approved upper facial lines indications)	Drooping of the eyelid, which may be technique-related, is consistent with the local muscle relaxant action of VISTABEL	Yes. The doctor's prescribing information provides administration instructions to reduce the risk of drooping of the eyelid.

Table 9–52 Important Potential Risks for BOTOX®

Risk	What is Known
All Indications	
Guillain-Barré syndrome (GBS)	Guillain-Barré Syndrome (GBS) is a disorder in which the body's immune system attacks part of the peripheral nervous system. Symptoms of this disorder include varying degrees of weakness or tingling sensations of the legs, arms and/or body. Cases of GBS following the use of BOTOX® have only been reported sporadically. There is currently no evidence to suggest an increased risk of experiencing GBS following the use of BOTOX®
Worsening of multiple sclerosis (MS) in patients who receive injections in the bladder wall to stop the involuntary leakage of urine ('urinary incontinence') due to a 'neurogenic' bladder ('neurogenic' means due to a nervous system disease or disorder such as myasthenia gravis or spinal cord injury) (Multiple sclerosis exacerbation)	A natural feature of any disease is that the patient may at times experience worsening of the disease itself, and this is also true for MS. True worsening of MS is an unpredictable event and mostly occurs without warning. Based on how BOTOX® works, it is unlikely that BOTOX® alone can cause a patient's MS to worsen. However, patients with MS may also experience what is called 'pseudo-exacerbation' (or 'fake' worsening) caused by infection, heat, or stress. Since the patients with MS who are being treated with BOTOX® are at a higher risk of developing urinary tract infections (UTIs), there is a potential for the UTIs to trigger 'pseudo-exacerbations' of MS.
Potential medication error, overdose from misuse of 200 U vial (*in those countries where the 200 U vial is available*)	BOTOX® is packaged in vials (small glass containers) of different sizes (a 50 U vial, a 100 Unit vial, and a 200 Unit vial). It is possible that a doctor could accidentally overdose a patient by taking the BOTOX® from a 200 Unit vial instead of one of the smaller ones.
Interaction with medicines that may cause an excessive effect of BOTOX® (Interaction with other neuromuscular junction-acting agents)	If certain medicines, such as antibiotics (used to treat infections), medicines that affect the nervous system, or medicines that relax muscles are used at the same time as BOTOX®, they may potentially cause excessive effects of BOTOX®, such as excessive muscle weakness.
Interaction with a medicine containing botulinum toxin (the active substance of BOTOX®) at the same time or within several months (Interaction with different botulinum toxin serotypes at the same time or within several months)	There are several medicines from companies other than Allergan that also contain botulinum toxin as the active ingredient. The other botulinum toxin products have similar effects as BOTOX®, so if they are too soon together a patient could potentially experience an excessive effect of BOTOX®, such as excessive muscle weakness.
Urinary Bladder Disorder Indications	

Risk	What is Known
Kidney infection ('pyelonephritis') in patients who receive injections in the bladder wall to stop the involuntary leakage of urine ('urinary incontinence') due to an overactive or 'neurogenic' bladder ('neurogenic' means due to a nervous system disease or disorder such as myasthenia gravis or spinal cord injury) (Pyelonephritis in patients with bladder disorders with urinary incontinence)	It is possible for infections in the bladder to worsen and travel from the bladder to other parts of the urinary tract, especially the kidney. Pyelonephritis rarely occurred in the clinical trials that studied BOTOX® for the treatment of urinary incontinence. Severe pyelonephritis was seen only in the neurogenic detrusor overactivity (NDO) trials. In the NDO trials, the number of pyelonephritis reports was similar between BOTOX® and placebo patients. In the overactive bladder (OAB) trials, moderate pyelonephritis was reported from one patient in the BOTOX® group and none from the placebo group.
Neurology (or Nervous system disorder) Indications	
Falls in adult patients with persistent muscle spasms of the ankle who have suffered a stroke (Falls in post-stroke patients with focal spasticity of the ankle)	For patients who may be more likely to fall, your doctor will judge if this treatment is suitable.

Table 9–53 Missing Information for BOTOX®

Risk	What is known
All Indications	
Pregnancy	The effects of BOTOX® on the fetus during pregnancy have not been studied in clinical trials. However, any report of BOTOX® use during pregnancy is closely monitored. To date, no association has been observed between BOTOX® and adverse pregnancy events, birth defects, or spontaneous abortions. The doctor's prescribing information recommends that BOTOX® should not be used in pregnancy women unless clearly necessary.
Breast feeding (Lactation)	The effects of BOTOX® on babies who are nursing has not been studied in clinical trials, and it is unknown if BOTOX® can be found in human milk. However, any report of BOTOX® use during breast feeding is closely monitored. To date, no association has been observed between BOTOX® and adverse events in babies who are breast feeding. The doctor's prescribing information recommends that BOTOX® should never be used in women who are breast feeding.
Urinary Bladder Disorder Indications	
Long-term use in male patients who receive injections in the bladder wall to stop the involuntary leakage of urine ('urinary incontinence') due to an overactive bladder (Long-term use in male patients with overactive bladder)	The clinical studies of BOTOX® for the treatment of urinary incontinence due to an overactive bladder did not include enough male patients to determine if they respond differently to BOTOX® than female patients, or if they have side effects particular to males only.
Neurology (or Nervous system disorder) Indications	
Use in patients who receive injections for the headache due to medication overuse (Use in patients with medication overuse headache [secondary headache disorder])	The clinical studies of BOTOX® for the treatment of chronic migraine did not study patients who received BOTOX® for the treatment of headache due to medication overuse.

VI.2.5 Summary of additional risk minimization measures by safety concern for BOTOX®

Additional risk minimization measures are in place for the identified risks of hypersensitivity reactions, distant spread of toxin, dysphagia in cervical dystonia and chronic migraine, urinary tract infection and urinary retention in NDO and OAB treatment, for the potential risk of overdose from the misuse of a 200 Unit vial, and for missing information concerning pregnancy and lactation.

Table 9–54 Allergic Reaction (Hypersensitivity)

Risk minimization measure: Patient Education	
Objective and rationale	To educate patients about the risk of a severe allergic reaction following treatment with BOTOX®
Summary description of main additional risk minimization measures	Patient educational materials (given to patients by their doctors) provide information regarding BOTOX® treatment, including possible side effects, and to contact your doctor immediately should you experience a severe allergic reaction (hives, swelling including swelling of the face/throat, wheezing, feeling faint and shortness of breath).

Table 9–55 Spread of BOTOX® Far Away From the Site of Injection (Distant Spread of Toxin)

Risk minimization measure: Healthcare Professional (HCP) and Patient Education	
Objective and rationale	To educate HCPs and patients about the risk of distant spread of toxin, and the appropriate management of this risk to minimize its occurrence and its severity
Summary description of main additional risk minimization measures	• Patient educational materials (given to patients by their doctors) explain the possible side effects of BOTOX® treatment, including the side effects involved in the distant spread of toxin. • The Patient Informed Consent (PIC) template for BOTOX® clinical studies includes an explanation of distant spread of toxin. This wording is included in all PICs for all Allergan-sponsored BOTOX® clinical studies. All subjects participating in Allergan-sponsored clinical studies are required to indicate their understanding of this document by signature before starting the study, and they are given a copy of it to refer to. • European doctors received a joint 'Dear Healthcare Professional Communication' in 2007 (when distant spread of toxin was first recognized as an important risk for all botulinum toxin products), and sales materials were revised to reflect changes in the doctor's prescribing information regarding distant spread of toxin. • The Investigator Brochure (IB) for Allergan-sponsored BOTOX® clinical studies contains up-to-date information for distant spread of toxin. This document is a review of BOTOX® efficacy and safety information, and it is prepared for and distributed to all doctors who participate in Allergan-sponsored clinical studies (the 'investigators'). Allergan tracks distribution and receipt of this document. • Allergan-sponsored training programs that include information regarding distant spread of toxin are available for persons qualified to administer BOTOX® (or 'injectors'). Also, before clinical studies begin, investigators receive training about distant spread of toxin at investigator meetings. • At appropriate scientific meetings, Allergan sets up booths with safety information for HCPs. This includes information regarding distant spread of toxin.

Table 9–56 Difficulty Swallowing (Dysphagia) in Patients Treated for Cervical Dystonia or Chronic Migraine

Risk minimization measure: Patient Education	
Objective and rationale	To educate patients about the risk of difficulty swallowing following treatment with BOTOX® for cervical dystonia or chronic migraine
Summary description of main additional risk minimization measures	Patient educational materials (given to patients by their doctors) provide information regarding BOTOX® treatment for cervical dystonia or chronic migraine, including possible side effects, and to contact your doctor immediately should you experience difficulty in swallowing.

Table 9–57 Urinary Tract Infection and Inability to Empty the Bladder (Urinary Retention) in Patients Receiving BOTOX® Injections in the Bladder Wall

Risk minimization measure: Patient Education	
Objective and rationale	To educate patients about the risk of urinary tract infection (UTI) and inability to empty the bladder (urinary retention) in patients who receive BOTOX® injections in the bladder wall to stop the involuntary leakage of urine (‘urinary incontinence’) due to an overactive or ‘neurogenic’ bladder (‘neurogenic’ means due to a nervous system disease or disorder such as multiple sclerosis or spinal cord injury)
Summary description of main additional risk minimization measures	Patient educational materials (given to patients by their doctors) provide information regarding BOTOX® treatment for overactive or neurogenic bladder, including possible side effects, and to contact your doctor immediately if you experience a urinary tract infection (a burning sensation on passing urine and a temperature over 38C) or the inability to empty your bladder (urinary retention).

Table 9–58 Potential Medication Error, Overdose from Misuse of a 200U Vial

Risk minimization measure: Healthcare Professional (HCP) Education	
Objective and rationale	To educate HCPs about the risk of possible overdose from misuse of the 200 Unit vial
Summary description of main additional risk minimization measures	• Allergan-sponsored training programs that include information regarding possible overdose due to misuse of the 200 Unit vial are available for persons qualified to administer BOTOX® (or 'injectors'). Also, before clinical studies begin, investigators who will use the 200 Unit vial in their studies receive similar training at investigator meetings. The following messages are communicated to the doctors: o Notification that a 200 Unit vial size is now available, including color illustrations of packaging. o Emphasis on color-coded text on the packaging to differentiate between product sizes. o Emphasis on color-coded aluminium crimp/plastic flip-off seal assembly to differentiate between the product sizes. o Caution to physicians to establish correct vial size prior to injecting. • The doctor's prescribing information has also been updated with specific information regarding the 200 Unit vial size and how to prevent accidental overdose from its misuse.

Table 9–59 Pregnancy

Risk minimization measure: Clinical Study Investigator and Patient Education	
Objective and rationale	To minimize exposure to BOTOX® during pregnancy in clinical studies by educating the doctors who conduct the studies (the 'investigators') and the patients who might become pregnant during the studies.
Summary description of main additional risk minimization measures	• A 'Dear Investigator' letter was sent to all active investigators in 2007 to advise that, in all current and future BOTOX® clinical studies, female patients who might possibly become pregnant during the study would be screened to be sure they were not pregnant before the study began and also before each BOTOX® treatment was given. • The Patient Informed Consent (PIC) template for BOTOX® clinical studies includes wording that all female patients who might possibly become pregnant during a BOTOX® study must use reliable contraception while participating in the study, and those that don't are excluded from participating. This wording is included in all PICs for all Allergan-sponsored BOTOX® clinical studies. All subjects participating in Allergan-sponsored clinical studies are required to indicate their understanding of this document by signature before starting the study, and they are given a copy of it to refer to.

VI.2.6 Planned Post-authorization Development Plan for BOTOX®

There are no studies that are a condition of the marketing authorization.

VI.2 Elements for a Public Summary for VISTABEL

VI.2.1 Overview of disease epidemiology for VISTABEL

9.24 Glabellar Frown Lines (Vertical Lines between the Eyebrows seen at Frown) and Lateral Canthus Lines (Crow's Feet Lines)

One of the first places on the face to show signs of aging is the area around the eye (the 'lateral canthus' area). It is estimated that 90-95% of Caucasian women and 25% of Asian women have noticeable lateral canthal lines (crow's feet lines) by the time they are 31-40 years old. Another early sign of ageing is glabellar frown lines, which are the ‘no. 11’ parallel lines between the eyebrows. It is estimated that 70% of Caucasian women and 20% of Asian women have noticeable glabellar frown lines by the time they are 31-40 years old. These two types of wrinkles most often occur together.

Ageing of the face results from the combined effects of 'atrophy' (wasting away of a part of the body) and a loss of fullness of the face, bone loss, decreased 'elasticity' (decreased ability of the skin to return to shape when stretched), and gravity. Ageing is also influenced by genetic factors, by environmental factors such as exposure to the sun or to the chemicals in cigarette smoke. With the skin loses elasticity, repeated facial expressions can become permanent lines. If the wrinkles are severe, they can affect the patient's quality of life.

VI.2.2 Summary of treatment benefits for VISTABEL

9.25 Glabellar Lines (Vertical Lines Between the Eyebrows) and Lateral Canthal Lines (Crow’s Feet Lines or Fan-Shaped Lines From the Corner of the Eyes)

Glabellar Lines (Vertical Lines Between the Eyebrows): In two studies (191622-010, 191622-023), patients with moderate to severe glabellar lines were treated with either 20 Units of VISTABEL (405 patients) or placebo (132 patients). The doctors who conducted these studies judged that the severity of glabellar lines was significantly reduced for up to 120 days in the VISTABEL group compared to the placebo group, and that 80% of VISTABEL-treated patients had responded to the treatment at 30 days after injection compared to 3% of placebo-treated patients. Also, at 30 days after treatment, 89% of VISTABEL-treated patients felt that they had moderate or better improvement of their wrinkles, compared to 7% of placebo-treated patients. After completing these studies, patients were able to enter the long-term continuation Study 191622-018 and receive repeat VISTABEL treatments at 120-day intervals. (The patients who

received placebo in the first two studies were switched to VISTABEL for the long-term continuation study.)

Lateral Canthal Lines (Crow's Feet Lines or Fan-Shaped Lines From the Corner of the Eyes): In two studies (191622-098, 191622-099), patients with moderate to severe crow's feet lines (CFL) were treated with either 24 Units of VISTABEL (528 patients) or placebo (529 patients). In Study 191622-099, an additional 305 patients were also treated with 44 U VISTABEL for the combined treatment of CFL and glabellar lines. After receiving 2 treatments and completing Study 191622-099, patients were able to enter the long-term continuation Study 191622-104 (The patients who received placebo in the first study were switched to VISTABEL or placebo for the long-term continuation study.). There was a statistically significant difference in the proportion of patients achieving a CFL severity rating of none or mild at maximum smile when measured by the physician and patient, favoring VISTABEL compared to placebo.

VI.2.3 Unknowns relating to treatment benefits for VISTABEL

Not applicable

VI.2.4 Summary of safety concerns for VISTABEL

Table 9–60 Important Identified Risks for VISTABEL

Risk	What is known	Preventability
All Indications		
Allergic reactions (Hypersensitivity reactions)	Allergic reactions have been rarely reported. Symptoms usually occur with a short time after injection, and can range from mild reactions such as hives to more serious reactions such as swelling of the face or throat, wheezing, feeling faint, shortness of breath, or severe skin problems. In some cases the more severe reactions can be life-threatening. There has been one report of death from 'anaphylaxis' (an extreme allergic reaction); it is unknown if this patient had the reaction to BOTOX® (same formulation as VISTABEL), lidocaine, or some other drug.	Yes. The doctor's prescribing information for VISTABEL states that it should not be used in patients allergic (hypersensitive) to botulinum toxin type A or the inactive ingredients of VISTABEL (human albumin and sodium chloride). Also, it is generally recognized that patients who have a history of asthma, hives, or allergies to other medications are at greater risk of having allergic reactions to medicines.
Patients who suffer from diseases of the nervous system that affect the muscles, such as myasthenia gravis (MG), Lambert-Eaton syndrome, amyotrophic lateral	There have been a small number of reports in the medical literature that patients with pre-existing neuromuscular disorders may have more severe side effects, especially	Yes. The doctor's prescribing information for VISTABEL warns of the possibility of more severe side effects in patients with pre-existing neuromuscular disorders, and recommends extreme

Risk	What is known	Preventability
sclerosis (Lou Gehrig's disease), or motor neuropathy (in which the muscles don't work correctly because of nerve problems) (Pre-existing neuromuscular disorders)	difficulty in swallowing (dysphagia) and problems breathing.	caution when using VISTABEL in these patients. It is possible that the risk of severe side effects can be reduced by using the lowest dose possible, and, in some cases, by more accurately injecting the muscles by using a medical instrument called an 'electromyograph' that helps to guide the injections.
Becoming resistant to the beneficial effects of VISTABEL (Immunogenicity, drug resistance and antibody formation)	If VISTABEL is given too often or the dose is too high, the body can produce substances called 'antibodies' which can reduce the beneficial effects of VISTABEL. However, it is still possible to have side effects even though the beneficial effects are reduced.	Yes. The doctor's prescribing information for VISTABEL recommends that doctors use the lowest doses possible as infrequently as possible.
Spread of VISTABEL far away from the site of injection (Distant spread of toxin)	Side effects in areas of the body far away from the site(s) of injection have been reported very rarely and include reactions such as muscle weakness, constipation, being unable to urinate, difficulty in swallowing, and food or drink accidentally going into the lungs (via the windpipe) instead of the stomach, which in some cases may lead to pneumonia. Patients are at a greater risk of this side effect if they are treated with higher than recommended doses.	Yes. The doctor's prescribing information for VISTABEL recommends that doctors use the lowest doses possible, and, in some cases, suggests the use of a medical instrument called an 'electromyograph' that helps to guide the injections so that they can be made more accurately.
Upper Facial Lines Indications		
Drooping of the eyelid following injections to the vertical lines between the eyebrows seen at maximum frown or to the fan-shaped lines from the corner of the eyes seen at maximum smile when treated alone or at the same time as vertical lines between the eyebrows seen at maximum frown (Eyelid ptosis in approved upper facial lines indications)	Drooping of the eyelid, which may be technique-related, is consistent with the local muscle relaxant action of VISTABEL	Yes. The doctor's prescribing information provides administration instructions to reduce the risk of drooping of the eyelid.

Table 9–61 Important Potential Risks for VISTABEL

Risk	What is Known
All Indications	
Guillain-Barré syndrome (GBS)	Guillain-Barré Syndrome (GBS) is a disorder in which the body's immune system attacks part of the peripheral nervous system. Symptoms of this disorder include varying degrees of weakness or tingling sensations of the legs, arms and/or body. Cases of GBS following the use of BOTOX® have only been reported sporadically. There is currently no evidence to suggest an increased risk of experiencing GBS following the use of BOTOX®
Worsening of multiple sclerosis (MS) in patients who receive injections in the bladder wall to stop the involuntary leakage of urine ('urinary incontinence') due to a 'neurogenic' bladder ('neurogenic' means due to a nervous system disease or disorder such as myasthenia gravis or spinal cord injury) (Multiple sclerosis exacerbation)	A natural feature of any disease is that the patient may at times experience worsening of the disease itself, and this is also true for MS. True worsening of MS is an unpredictable event and mostly occurs without warning. Based on how BOTOX® works, it is unlikely that BOTOX® alone can cause a patient's MS to worsen. However, patients with MS may also experience what is called 'pseudo-exacerbation' (or 'fake' worsening) caused by infection, heat, or stress. Since the patients with MS who are being treated with BOTOX® are at a higher risk of developing urinary tract infections (UTIs), there is a potential for the UTIs to trigger 'pseudo-exacerbations' of MS.
Interaction with medicines that may cause an excessive effect of VISTABEL (Interaction with other neuromuscular junction-acting agents)	If certain medicines, such as antibiotics (used to treat infections), medicines that affect the nervous system, or medicines that relax muscles are used at the same time as VISTABEL, they may potentially cause excessive effects of VISTABEL, such as excessive muscle weakness.
Interaction with a medicine containing botulinum toxin (the active substance of VISTABEL) at the same time or within several months (Interaction with different botulinum toxin serotypes at the same time or within several months)	There are several medicines from companies other than Allergan that also contain botulinum toxin as the active ingredient. The other botulinum toxin products have similar effects as VISTABEL, so if they are too soon together a patient could potentially experience an excessive effect of VISTABEL, such as excessive muscle weakness.

Table 9–62 Missing Information for VISTABEL

Risk	What is known
All Indications	
Pregnancy	The effects of VISTABEL on the fetus during pregnancy have not been studied in clinical trials. However, any report of VISTABEL use during pregnancy is closely monitored. To date, no association has been observed between VISTABEL and adverse pregnancy events, birth defects, or spontaneous abortions. The doctor's prescribing information recommends that VISTABEL should not be used in pregnancy women unless clearly necessary.

Breast feeding (Lactation)	The effects of VISTABEL on babies who are nursing has not been studied in clinical trials, and it is unknown if VISTABEL can be found in human milk. However, any report of VISTABEL use during breast feeding is closely monitored. To date, no association has been observed between VISTABEL and adverse events in babies who are breast feeding. The doctor's prescribing information recommends that VISTABEL should never be used in women who are breast feeding.

VI.2.5 Summary of additional risk minimization measures by safety concern for VISTABEL

Additional risk minimization measures are in place for the identified risks of hypersensitivity reactions, distant spread of toxin, and for missing information concerning pregnancy and lactation.

Table 9–63 Allergic Reaction (Hypersensitivity)

Risk minimization measure: Patient Education	
Objective and rationale	To educate patients about the risk of a severe allergic reaction following treatment with VISTABEL
Summary description of main additional risk minimization measures	Patient educational materials (given to patients by their doctors) provide information regarding VISTABEL treatment, including possible side effects, and to contact your doctor immediately should you experience a severe allergic reaction (hives, swelling including swelling of the face/throat, wheezing, feeling faint and shortness of breath).

Table 9–64 Spread of VISTABEL Far Away From the Site of Injection (Distant Spread of Toxin)

Risk minimization measure: Healthcare Professional (HCP) and Patient Education	
Objective and rationale	To educate HCPs and patients about the risk of distant spread of toxin, and the appropriate management of this risk to minimize its occurrence and its severity
Summary description of main additional risk minimization measures	• Patient educational materials (given to patients by their doctors) explain the possible side effects of VISTABEL treatment, including the side effects involved in the distant spread of toxin. • The Patient Informed Consent (PIC) template for VISTABEL clinical studies includes an explanation of distant spread of toxin. This wording is included in all PICs for all Allergan-sponsored VISTABEL clinical studies. All subjects participating in Allergan-sponsored clinical studies are required to indicate their understanding of this document by signature before starting the study, and they are given a copy of it to refer to. • European doctors received a joint 'Dear Healthcare Professional Communication' in 2007 (when distant spread of toxin was first recognized as an important risk for all botulinum toxin products), and sales materials were revised

Risk minimization measure: Healthcare Professional (HCP) and Patient Education	
	to reflect changes in the doctor's prescribing information regarding distant spread of toxin. • The Investigator Brochure (IB) for Allergan-sponsored VISTABEL clinical studies contains up-to-date information for distant spread of toxin. This document is a review of VISTABEL efficacy and safety information, and it is prepared for and distributed to all doctors who participate in Allergan-sponsored clinical studies (the 'investigators'). Allergan tracks distribution and receipt of this document. • Allergan-sponsored training programs that include information regarding distant spread of toxin are available for persons qualified to administer VISTABEL (or 'injectors'). Also, before clinical studies begin, investigators receive training about distant spread of toxin at investigator meetings. • At appropriate scientific meetings, Allergan sets up booths with safety information for HCPs. This includes information regarding distant spread of toxin.

Table 9–65 Pregnancy

Risk minimization measure: Clinical Study Investigator and Patient Education	
Objective and rationale	To minimize exposure to VISTABEL during pregnancy in clinical studies by educating the doctors who conduct the studies (the 'investigators') and the patients who might become pregnant during the studies.
Summary description of main additional risk minimization measures	• A 'Dear Investigator' letter was sent to all active investigators in 2007 to advise that, in all current and future VISTABEL clinical studies, female patients who might possibly become pregnant during the study would be screened to be sure they were not pregnant before the study began and also before each VISTABEL treatment was given. • The Patient Informed Consent (PIC) template for VISTABEL clinical studies includes wording that all female patients who might possibly become pregnant during a VISTABEL study must use reliable contraception while participating in the study, and those that don't are excluded from participating. This wording is included in all PICs for all Allergan-sponsored VISTABEL clinical studies. All subjects participating in Allergan-sponsored clinical studies are required to indicate their understanding of this document by signature before starting the study, and they are given a copy of it to refer to.

VI.2.6 Planned Post-authorization Development Plan for VISTABEL

There are no studies that are a condition of the marketing authorization.

VI.2.7 Summary of Changes to Risk Management Plan Over Time

Table 9–66 Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
EU-RMP v7.3	Oct-2014	No new safety concerns	Update to address requests from Reference Authority (Ireland) during assessment of version 7.2 (EU worksharing procedure IE/H/xxxx/WS/006)
EU-RMP v7.3	Sep-2014	No new safety concerns	Update to address requests from Reference Authority (Ireland) and CMS (France, Italy and Netherlands) during assessment of version 7.2 (EU worksharing procedure IE/H/xxxx/WS/006)
EU-RMP v7.2	May-2014	**Addition of Important Potential Risk:** Falls in adult post-stroke patients with focal spasticity of the ankle **Reinstated Important Potential Risk:** Guillain-Barre syndrome **Addition of Missing Information:** Use in patients with medication overuse headache (secondary headache disorder)	Update to address requests from MHRA and MRP during lower limb spasticity review
EU-RMP v7.1	Dec-2013	**Addition of Important Identified Risk:** Eyelid ptosis in approved upper facial lines indications	Update to address requests from MRP during lateral canthal lines reviews
EU-RMP v7.0	May-2013	**Addition of Missing Information:** Long term use in male patients with overactive bladder **Removal of Important Potential Risks:** Propose to remove Seizure, Cardiovascular events, Death and Guillain-Barre syndrome based on cumulative analyses **Removal of Missing Information:** Propose to remove renal and hepatic impairment based on analysis and pharmacological properties of BOTOX®	Update to address requests from Denmark, Netherlands Update to include lower limb spasticity data See Annex 12.7 on justification for removal of Important Potential Risks
EU-RMP v6.0	Oct-2012	No new safety concerns	Updated to include lateral canthal lines data
FR-RMP v4.3	Apr-2012	No new safety concerns	Updated to address AFSSAPS request
AU-RMP v5.0	Jun-2012	**Revised Important Identified Risks:** Urinary	Updated to include overactive

Version	Date	Safety Concerns	Comment
EU-RMP v5.0	Mar-2012	Tract Infection in patients with bladder disorders with urinary incontinence Urinary Retention in patients with bladder disorders with urinary incontinence **Revised Important Potential Risk:** Pyelonephritis in patients with bladder disorders with urinary incontinence	bladder data
EU-RMP v4.2	Feb-2012	No new safety concerns	Updated to incorporate updates from EU-RMPs v3.0.3, 3.0.4 and 4.1
EU-RMP v4.1	Jul-2011	**Addition of Important Potential Risk:** Multiple Sclerosis Exacerbation	Updated to address MHRA request
EU-RMP v4.0	Oct-2010	**Reclassified to Important Identified Risk:** Urinary Tract Infection in Neurogenic Detrusor Overactivity Urinary Retention in Neurogenic Detrusor Overactivity **Addition of Important Potential Risks:** Pyelonephritis	Updated to include neurogenic detrusor overactivity data
EU-RMP v3.0.4	Feb-2011	No new safety concerns	Updated to address IMB request
EU-RMP v3.0.3	Jan-2011	No new safety concerns	Updated to address IMB request
AU-RMP v3.2	Aug-2010	**Addition of Important Potential Risks:** Interaction with Other Neuromuscular Junction Acting Agents Interaction with Different Botulinum Toxin Serotypes at the Same Time or Within Several Months	Updated to address TGA request
EU-RMP v3.0.2	Jun-2010	**Addition of Important Identified Risk:** Worsening or Intractable Migraine/ Headache in Chronic Migraine Treatment	Updated to address MHRA request
EU-RMP v3.0.1	May-2010	**Addition of Important Identified Risk:** Immunogenicity, Drug Resistance and Antibody Formation **Addition of Important Potential Risk:** Death **Revised Important Identified Risks:** Dysphagia in Chronic Migraine and Cervical Dystonia Distant Spread of Toxin **Removed Important Missing Info:** Drug utilization/Current Treatment Practice **Revised Important Potential Risk:** Overactive Bladder as Off-Label	Updated to address MHRA request
AU-RMP v3.1	Oct-2009	No new safety concerns	Updated to address TGA request

Version	Date	Safety Concerns	Comment
EU-RMP v3.0	Aug-2009	**Revised Important Potential Risk:** Dysphagia in Chronic Migraine	Updated to include chronic migraine data
EU-RMP v2.0	Feb-2009	**Addition of Important Potential Risks:** Urinary Tract Infection in Neurogenic Detrusor Overactivity Urinary Retention/Post Void Residual Volume in Neurogenic Detrusor Overactivity Patients Medication Error, Overdose from Misuse of 200 U vial **Removal of Important Identified Risks:** Immunogenicity, Drug Resistance and Antibody Formation Dysphagia **Removal of Important Potential Risks:** Bladder Stones Death **Removal of Important Missing Info:** Pediatric Use Geriatric Use **Revised Important Potential Risk:** Possible Distant Spread of Toxin	Updated to include a late-stage development indication, neurogenic detrusor overactivity
EU-RMP v1.0	Sep-2007	**Addition of Important Identified Risks:** Hypersensitivity Reactions Immunogenicity, Drug Resistance and Antibody Formation Dysphagia **Addition of Important Potential Risks:** Bladder Stones Spread of Toxin Seizure Cardiovascular Disorders Death Guillain-Barre Syndrome **Addition of Important Missing Info:** Pregnancy Lactation Pediatric Use Geriatric Use Use in Patients with Renal or Hepatic Impairment Drug utilization/Current Treatment Practice	Updated to address IMB and AFSSAPS request
EU-RMP	Oct-2006	**Important Identified Risk:** Pre-existing Neuromuscular Disorders **Important Potential Risk:** Distant Effects (Potential Spread Reactions)	Request from Pharmacovigilance Working Party (PhVWP), IMB and AFSSAPS to address spread of toxin concern across all *Clostridium botulinum* toxins