6.2 Elements for a Public Summary

6.2.1 Overview of disease epidemiology

6.2.1.1 Limb spasticity following a stroke in adults

In the EU, stroke occurs in approximately 11 people in every 10 000. Spasticity is an unusual tightness or stiffness of muscles and occurs in approximately 19 to 43% of stroke patients. There is a greater risk of stroke occurring in men than in women, yet more strokes occur in women due to their longer life span. Afro-Caribbean individuals are twice as likely to have a stroke compared to Caucasian individuals. Risk factors for stroke include age, smoking, obesity, high blood pressure, diabetes, atrial fibrillation (a type of abnormal heart rhythm) and high cholesterol.

Annually, stroke accounts for over 460 000 deaths in the EU. Post-stroke muscle weakness and abnormal muscle tone is a major cause of disability. Treatment of spasticity following a stroke may include any or a combination of physical and occupational therapy, medication (injected and oral) and surgery.

6.2.1.2 Spastic equinus foot deformity due to cerebral palsy in children over 2 years of age

Cerebral palsy is a persistent but unchanging movement disorder that usually occurs in children as a result of problems during pregnancy or birth. It is a relatively rare condition, with approximately 2 people in every 1000 affected the UK. Spastic equinus foot is the most common leg deformity in children with cerebral palsy. Certain muscles in the lower limbs are permanently contracted, causing difficulty walking and increased risk of falls.

Many patients with a mild form of disease have a normal life expectancy. However, a child with severe disease has only a 40% chance of living to the age of 20 years. Approximately half of individuals with cerebral palsy use assistive devices including braces, walkers and wheelchairs to aid mobility. Cases of more severe cerebral palsy may be associated with lower intelligence in the affected patients.

Treatment may include physiotherapy, surgical intervention, continuous pump-administered muscle relaxants and injections of botulinum toxin into the affected muscles.

6.2.1.3 Spasmodic torticollis (cervical dystonia)

Spasmodic torticollis is a painful condition that causes involuntary neck movements in a certain direction. In the EU, spasmodic torticollis occurs in approximately 57 people in every million. The disease can occur at any age (most commonly between the ages of 20 and 49 years) and is more common in women. Occurrence of spasmodic torticollis or other types of abnormal muscle tone in an individual's family increases the risk of developing the disease.

Spasmodic torticollis has a significant negative impact on quality of life and may lead to the development of similar symptoms in muscles adjacent to the neck.

Currently, there is no cure for spasmodic torticollis. Treatment focuses on relieving the signs and symptoms, and includes medication (including muscle relaxants and pain medication), therapy (physiotherapy, stress management techniques), or surgery (when other treatments fail). Injections of botulinum toxin into the affected muscles usually results in immediate improvement for the majority of individuals.

6.2.1.4 Blepharospasm in adults

Blepharospasm is an involuntary contraction of the eye muscles, where the eye may blink more frequently and/or close altogether for minutes at a time. In Europe, blepharospasm occurs in approximately 16 to 133 people in every million. The disease can occur at any age (most commonly between the ages of 50 and 70 years) and is more common in women. Risk factors include family history of the disease, and certain environmental factors (smoking, sunlight) in combination with genetic factors, although this is not fully understood.

Although rarely associated with eye pain, involuntary eye closing may interfere with an individual's routine and social life.

Regular botulinum toxin injections around the eye usually results in near-immediate relief of symptoms for the majority of patients. Other treatment may include oral medications (although none are currently approved), surgical intervention (when other treatments are ineffective), sensory aids, stress management, and support groups.

6.2.1.5 Hemifacial spasm in adults

Hemifacial spasm is repetitive, irregular twitching of facial muscles on 1 side of the face. Although it is difficult to estimate (due to lack of information, underdiagnosis and misdiagnosis), approximately 10 people in every 100 000 are thought to be affected. Patients usually develop spasms in their 40s and 50s and women are twice as likely to develop them than men. Spasms can spread to other areas of the face over time, including the other side of the face. The most common trigger is compression of facial nerves (due to many causes; e.g., injury, stroke, multiple sclerosis).

Hemifacial spasm can cause social embarrassment, and visual and verbal disability.

For most patients, the treatment of choice is injection of botulinum toxin. Other treatment may include medication (e.g. anti-convulsants), surgical intervention (to reduce pressure on the facial nerve), sensory trick, exercise, relaxation techniques, stress management and support groups.

6.2.1.6 Axillary hyperhidrosis in adults

Axillary hyperhidrosis is excessive sweating of the underarms. The number of people affected is difficult to determine as many people do not seek treatment. Increased sweating may be caused by many factors, including anxiety, increased weight, certain skin disorders (e.g., psoriasis), low blood sugar levels, and some neurological disorders. A family history of hyperhidrosis also increases the chance of an individual experiencing the same symptoms, which usually begin in puberty.

Severe hyperhidrosis can cause extreme embarrassment that may lead to social and professional isolation. Other complications include infections and inflammation of the skin.

Management of axillary hyperhidrosis is usually via applications of various medications (e.g., aluminium chloride) or regular injections of botulinum toxin into the affected areas. Removal of the sweat glands by surgery can also be used, but carries with it a risk of scarring.

6.2.1.7 Moderate to severe glabellar lines in adults

As people continue to live longer, there is an increasing number of people who develop wrinkles between the eyebrows, due to increased or continuous facial muscle contraction. These wrinkles are a major source of worry for some patients and may lead to depression and other emotional instability, including low self-esteem. For these reasons, there is an increasing demand for the treatment of glabellar lines.

6.2.1.8 Spasticity of the arms and/or legs in adults and leg spasticity in children aged 2 years and over

Spasticity is an unusual tightness or increased muscle tone, making muscles stiff and rigid. The condition can interfere with walking, movement and speech. It can be caused by many factors, such as spinal cord injury, multiple sclerosis, stroke, cerebral palsy, and traumatic brain injury.

Spasticity has a negative impact on patients, causing pain, pressure sores and contractures. Often the disease limits activity, creates a dependence on caregivers and restricts an individual's participation in social and family life. Overall, spasticity may result in a significant decrease in quality of life.

Management of spasticity is achieved by a combination of treatments, including physiotherapy, local injections of botulinum toxin, oral medications or continuous pump-administered muscle relaxants. There is a rare need for surgical correction; this is usually only performed in extreme cases.

6.2.2 Summary of treatment benefits

Dysport causes muscle relaxation and can be used to treat conditions resulting from prolonged muscle contractions (e.g. blepharospasm, hemifacial spasm, spasmodic torticollis [neck spasticity], arm and leg spasticity frown lines, and leg spasticity in children with cerebral palsy). Dysport can also be used to reduce the stimulation of the sweat glands in patients with excessive sweating under the armpits (axillary hyperhidrosis).

Completed Ipsen clinical studies to establish the benefit of Dysport in the treatment of blepharospasm, hemifacial spasm, spasmodic torticollis, arm and leg spasticity, glabellar lines and axillary hyperhidrosis (in adults) and leg spasticity (in children) have included 6948 people.

Blepharospasm (and hemifacial spasm)

The effectiveness of Dysport in the treatment of blepharospasm (and hemifacial spasm) in approximately 337 subjects showed that treatment with Dysport resulted in up to 89% improvement in visual function.

Spasmodic torticollis

Studies in approximately 1217 subjects to evaluate the efficacy of Dysport in spasmodic torticollis showed that Dysport improved posture, reduced pain and increased the range of motion of the neck and showed superior efficacy over placebo in subjects with spasmodic torticollis.

Adult arm and leg spasticity

Studies in approximately 1219 subjects to assess the efficacy of Dysport in arm and leg spasticity showed that administration of Dysport reduced pain and dependence on walking aids.

Axillary hyperhidrosis

Key studies that assessed the efficacy of Dysport in approximately 189 subjects with axillary hyperhidrosis showed that Dysport reduced sweating with maintained efficacy and improved the quality of life of the patients.

Glabellar lines

In the key clinical studies in approximately 3342 subjects, Clostridium botulinum toxin type A - haemaglutinin complex (BTX-A-HAC) injections significantly reduced the severity of glabellar lines for up to 4 months. Data from these studies showed that 90% of patients responded to treatment with Dysport.

Leg spasticity in children

Key studies that assessed the efficacy of Dysport in approximately 666 paediatric subjects with leg spasticity showed that Dysport improved muscle tone and spasticity and functional improvement of the patients.

6.2.3 Unknowns relating to treatment benefits

No significant unknown information relating to treatment benefits of Dysport in the licensed indications has been identified by the Company.

6.2.4 Summary of safety concerns

The important identified risks and missing information for Dysport are summarised in Table 1 and Table 2.

Table 1: Important identified risks – Summary

Risk	What is known	Preventability
Remote distribution of the effects of the toxin	Serious but reversible reactions in muscles other than those targeted by the administration of Dysport can occur, although the risk is considered to be low.	Clinicians are advised about the possibility of such undesirable effects and how to reduce the likelihood of occurrence, especially in patients with pre-existing risk factors.

Table 2: Missing information – Summary

Risk	What is known
Use in pregnancy and lactation	The experience with Dysport in pregnant and breastfeeding women is limited. The Company continuously assesses all reports relating to the use of Dysport in pregnant and breastfeeding women.
Use in children aged <2 years for leg spasticity and use in children <18 years for all other (i.e. unapproved) indications	The experience with Dysport in children outside licensed use in children with leg spasticity is limited. The Company is currently conducting studies in spasticity of the upper and lower limbs in children.

6.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics, which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet. The measures in these documents are known as routine risk minimisation measures.

6.2.6 Planned Post-authorisation Development Plan

Not applicable.

6.2.7 Summary of changes to the Risk Management Plan over time

A summary of the major changes to the RMP is provided in Table 3.

Table 3: Major changes to the RMP over time

Version	Date	Safety concerns	Comment
1.0	Data Lock Point 31 October 2006	**Important Identified Risks:** – Events potentially related to local and remote distribution of toxin effect **Important Potential Risks:** – None **Missing Information:** – None	None.
2.1	Data Lock Point 30 September 2009	The important identified risk of 'events potentially related to local and remote distribution of toxin effect' was updated to 'distribution of effects of the toxin to sites remote from site of administration'.	None.
3.0	Data Lock Point 09 August 2013	Addition of "Use in pregnancy and lactation" as missing information. Addition of " Use in children aged <2 years for leg spasticity due to cerebral palsy and local symptomatic treatment for spasticity affecting the lower limbs; and use in children <18 years for all other (ie unapproved) indications" as missing information. Removal of information relating the indication of "Lateral canthal lines". Alignment of the RMP with the new European Guideline (EMA/816292/2011) on Good Pharmacovigilance Practices (Module V). Update of the risk minimisation sections following the results of the Risk Minimisation Effectiveness Survey.	Reformatting of existing RMP into new template.
4.0	Data Lock Point 09 August 2013	Removal of educational material. The impact of this educational material was assessed and the conclusion reached that it had little effect on factors that would influence spread effect (e.g. physician's knowledge). Since these additional educational materials showed no benefit it was decided that information routinely provided (such as SmPC and PIL) would be appropriate since all relevant information on spread effect is comprehensively detailed in these documents.	Release from FUM.SE_H_283_01_FU_03
5.0	Data Lock Point 31 July 2015	Update of Module III, including removal of exposure data from ongoing studies. Update of Module SVI – Additional EU requirements for the safety specification.	None.

Note: EMA = European Medicines Agency, EU = European Union, PIL = Product Information Leaflet, RMP = Risk Management Plan, SmPC = Summary Product Characteristics