VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Xeomin

In the scientific literature there is limited data about the occurrence of the diseases for which Botulinum Toxin A is approved. Data vary from 5 to 18 patients per 100.000

people for cervical dystonia and spasticity of the upper limb after stroke. 0.80 patients per 100.000 person-years come down with cervical dystonia. Up to 13 patients per 100.000 people suffer from blepharospasm. It is unknown how much patients come down with blepharospasm and spasticity of the upper limb after stroke per 100.000 person-years.

Bocouture

For upper facial lines (glabellar frown lines, lateral periorbital lines, and horizontal forehead lines) no data is published.

VI.2.2 Summary of treatment benefits

Xeomin

Cervical dystonia

Cervical dystonia is characterised by involuntary, inappropriate neuromuscular hyperactivity in a small number of relatively easily accessible muscles of the neck and shoulder, which leads to abnormal head movements and postures, and may cause significant disability and pain. The standard treatment for cervical dystonia is regular injections of Botulinum toxin. Botulinum toxin has been shown to be a highly effective and well-tolerated symptomatic treatment of focal dystonia. In controlled studies it has been shown to markedly improve pain and postural deviation in 60-80% of subjects with cervical dystonia.

So far, 431 subjects have been treated with single dose treatment of NT 201, 244 with comparator and 74 with placebo during clinical trials, 286 subjects have been treated with repeated dose. Statistically significant and clinically meaningful benefit compared to placebo was observed. The therapeutic effect is a localised muscle weakness with potential side effects not affecting the whole body.

Blepharospasm

Blepharospasm is a progressive disease characterised by spontaneous, spasmodic, bilateral, intermittent or persistent involuntary contractions of the orbicularis oculi muscles (muscle around the eye). Botulinum toxin is the first-line treatment for blepharospasm (eyelid spasm). Given as a local injection, Botulinum toxin type A is a highly effective and well-tolerated symptomatic treatment of blepharospasm. Most subjects who receive Botulinum toxin treatment for blepharospasm experience substantial relief of their symptoms.

So far, 222 subjects have been treated with single dose treatment of NT 201, 152 with comparator and 34 with placebo during clinical trials, 102 subjects have been treated with repeated dose. Statistically significant and clinically meaningful benefit compared to placebo was observed. The therapeutic effect is a localised muscle weakness with potential side effects not affecting the whole body.

Post-stroke spasticity of the upper limb

The standard therapy for spasticity includes physiotherapy, occupational therapy, and rehabilitation treatments such as splinting, all of which are usually well tolerated. Other treatments include oral drugs such as benzodiazepines or other so-called muscle relaxants, but their use is limited by relevant side effects which may affect the whole body (so called systemic side effects such as low blood pressure, drowsiness etc.). The reason for this is that these drugs are non-selective in their action and may weaken also non-spastic muscles. Further non-oral treatments could be alcohol or phenol injections that are used for long-term chemical destruction of peripheral nerve. Main side effects related to these injections are pain (pain during injection, chronic pain) and the blood vessels around the injection may be affected because of the toxicity of these substances. Surgery can be used to lengthen tendons, but involves the risk of general anaesthesia and the anatomical changes are permanent.

So far, 475 subjects have been treated with single dose treatment of NT 201 and 182 with placebo during clinical trials, 441 subjects have been treated with repeated dose. Response rates of more than 60% were observed with NT 201. The therapeutic effect is a localised muscle weakness with potential side effects not affecting the whole body.

As of December 31st, 2014, NT 201 is approved in 45 countries worldwide for a variety of different indications: 31 EU/EEA countries (including Germany) and 14 other countries including USA and Canada. The different national approvals worldwide cover the treatment of several disorders of the nervous system including cervical dystonia, blepharospasm and spasticity. NT 201 is marketed under the trade name Xeomin/Xeomeen for treatment of cervical dystonia. The first marketing authorisation for Xeomin was granted by the German regulatory authority on 31 May 2005 in two neurological disorders, and extended to the indication spasticity. Since its first launch on 01 July 2005, Xeomin has so far been received by nearly 795.000 persons in studies and in the market.

Bocouture

Glabellar frown lines

Glabellar frown lines between the eyebrows are caused by contraction of the *corrugator muscle* located above both eyebrows and the *procerus muscle* at the root of the nose. Effective management of facial lines requires approaches including aesthetic and surgical dermatological treatments such as peels, laser resurfacing, fillers, and surgical treatments namely face lifting, eyebrow lift, and blepharoplasty (plastic surgery operation for correcting defects, deformities, and disfigurations of the eyelids). Since surgical techniques involve risks and recovery time, and rejuvenation and filler techniques may not achieve fully satisfactory results, local injection treatment with Botulinum toxin A rapidly became the standard treatment when the first representative of this drug class was approved for treatment of glabellar frown lines. The Botulinum toxin A complex preparation *Botox Cosmetic*® received approval for the treatment of glabellar frown lines in more than 20 countries including the USA. In several clinical studies, Botulinum toxin

type A complex preparations have been shown to be a highly effective and well-tolerated treatment for glabellar frown lines.

Small amounts of this toxin have been found to smooth out facial wrinkles with few side effects. Botulinum toxin stops muscle contractions by blocking a normal nerve-ending response without interfering with the muscles or the nerve itself. By blocking the nerves that move the muscles, Botulinum toxin may lessen how severe these lines appear and may even help prevent their development.

So far, 1067 subjects have been treated with single dose treatment of NT 201, 97 with a comparator and 316 with placebo, during clinical trials, 855 subjects have been treated with repeated dose. All clinical studies with NT 201 in subjects with moderate to severe glabellar frown lines or lateral periorbital lines conducted so far with maximum doses of up to 30 U, showed good efficacy as assessed by the investigator and the treated subjects as well with no new safety concerns. The effect of improving wrinkle severity lasted over a period of about 12 weeks in approximately 85% of the subjects.

In Germany NT 201 has been marketed since 15 Sep 2009 for glabellar frown lines and after 03 Jul 2014 for periorbital lines under the trade name Bocouture. So far Bocouture has been received by nearly 275,000 subjects in studies and in the market.

Lateral periorbital lines (crow`s feet lines)

Lateral periorbital lines are small wrinkles radiating outward from the outer corner of the eye. Other treatment options for lateral periorbital lines include dermal cosmetic treatments like peels, laser resurfacing, fillers, fat injections and surgical treatment such as rhytidectomy, facelift and blepharoplasty (plastic surgery operation for correcting defects, deformities, and disfigurations of the eyelids). Small amounts of toxin have been found to smooth out facial wrinkles with few side effects.

The clinical study with NT 201 in subjects with moderate to severe lateral periorbital lines (83 patients treated with NT 201, 28 with placebo) with a maximum dose of up to 24 U showed good efficacy and no new safety concerns. The therapeutic effect is a localised muscle weakness with potential side effects not affecting the whole body. As the effect will only last up to three months potential side effects are reversible.

In Germany NT 201 has been marketed since 15 Sep 2009 for glabellar frown lines and after 03 Jul 2014 for lateral periorbital lines under the trade name Bocouture. So far Bocouture has been received by nearly 275,000 subjects in studies and in the market.

Upper facial lines

Upper facial lines include small wrinkles radiating outward from the outer corner of the eye (lateral periorbital lines), vertical lines between the eyebrows (glabellar frown lines) and horizontal forehead lines. Other treatment options for upper facial lines include dermal cosmetic treatments like peels, laser resurfacing, fillers, fat injections and surgical treatment such as rhytidectomy, facelift and blepharoplasty (plastic surgery operation for

correcting defects, deformities, and disfigurations of the eyelids). Small amounts of toxin have been found to smooth out facial wrinkles with few side effects.

The clinical study with NT 201 in subjects with moderate to severe upper facial lines (105 patients treated with NT 201 single dose, 51 patients with placebo, 139 patients with repeated dose) with a maximum dose of up to 64 U showed good efficacy and no new safety concerns. The therapeutic effect is a localised muscle weakness with potential side effects not affecting the whole body. As the effect will only last up to three months potential side effects are reversible.

In Germany NT 201 has been marketed since 15 Sep 2009 for glabellar frown lines and after 03 Jul 2014 for periorbital lines under the trade name Bocouture. So far Bocouture has been received by nearly 275.000 subjects in studies and in the market.

VI.2.3 Unknowns relating to treatment benefits

Xeomin

In the clinical studies most subjects were white Caucasians with a mean age of 51 years (cervical dystonia), 62 years (blepharospasm) and 58 years (spasticity) with an age range from 18 to 87 years. There is no evidence to suggest that results would be any different in non-white subjects or in younger or older subjects.

Bocouture

In the clinical studies most patients were white Caucasians with a mean age of 45 years (glabellar frown lines), 47 years (lateral periorbital lines) and 47 years (upper facial lines) with an age range from 21 to 82 years. There is no evidence to suggest that results would be any different in non-white patients or in younger or older patients.

VI.2.4 Summary of safety concerns

Important identified risks

Xeomin

Risk	What is known	Preventability
Distant or local toxin spread (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 tiredness, loss of strength and muscle weakness (paralysis) all over the body, double vision, blurred vision, drooping eyelids, swallowing difficulties, trouble saying words clearly, loss of bladder control, and breathing difficulties. These symptoms	The recommended dosage of Botulinum toxin should not be exceeded. Instructions given in the SmPC regarding application techniques should be carefully observed. Usually, undesirable effects are reported within the first week after treatment. Therefore, an increased awareness on the part of the treating physician, as well

Risk	What is known	Preventability
	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 the spread of toxin effects.	as of the subject during this time period, is of paramount importance.
Swallowing difficulties (dysphagia)	Swallowing difficulties have been reported following injection to sites other than the injected muscles. Swallowing difficulties may persist for several months, and people who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving Botulinum toxin have the highest risk of experiencing these problems.	The recommended dosage of Botulinum toxin should not be exceeded. Instructions given in the SmPC regarding application techniques should be carefully observed. Usually, undesirable effects are reported within the first week after treatment. Therefore, an increased awareness on the part of the treating physician, as well as of the subject during this time period, is of paramount importance Subjects who already had swallowing difficulties or breathing problems before should be treated with Xeomin with extreme caution. The injection of Bocouture is not recommended for patients with a history of dysphagia. These precautionary statements are referred to in the SmPC.
Hypersensitivity	Hypersensitivity reactions have been reported with Botulinum toxin products including severe allergic reactions, hives (urticaria), swelling of soft tissue, and shortness of breath. If serious and/or immediate hypersensitivity reactions occur further injection of Botulinum toxin should be discontinued and appropriate medical therapy immediately instituted.	Instructions given in the SmPC and the Investigator's Brochure regarding contraindications and possible side effects should be carefully observed. Appropriate medical therapy should be available if anaphylactic and/or immediate hypersensitivity reactions occur. Subjects should contact medical aid immediately if experiencing difficulty with breathing, swallowing or speaking due to the swelling of the face, lips mouth or throat, hives, swelling of hand, feet or ankles. These precautions are explicitly referred to in the SmPC resp. in the package leaflet.

Risk	What is known	Preventability
Formation of antibodies	Risk factors for antibody-induced therapy failure include the amount of Botulinum toxin applied at each injection series and the interval between injections. Too frequent doses can increase the risk of antibody formation which may lead to treatment failure.	The treatment period between each treatment session should be maintained as referred in the SmPC.
Worsening of pre-existing neuromuscular disease	Botulinum toxin stops muscle contractions by blocking a normal nerve-ending response without interfering with the muscles or the nerve itself. The neuromuscular disease *amyotrophic lateral sclerosis* is a debilitating disease characterised by rapidly progressive muscle weakness which may be increased by Botulinum toxin.	Subjects with general disorders of muscle activity (e.g. Lambert-Eaton syndrome, myasthenia gravis) should be excluded from the treatment. Subjects suffering from Amyotrophic lateral sclerosis or other diseases which result in peripheral neuromuscular disorder should be treated with caution and have to be monitored very closely when administered Botulinum toxin. These conditions are explicitly referred to in the SmPC.
Bocouture		
Distant or local toxin spread (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 tiredness, loss of strength and muscle weakness (paralysis) all over the body, double vision, blurred vision, drooping eyelids, swallowing difficulties, trouble saying words clearly, loss of bladder control, 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 the spread of toxin effects.	The recommended dosage of Botulinum toxin should not be exceeded. Instructions given in the SmPC regarding application techniques should be carefully observed. Usually, undesirable effects are reported within the first week after treatment. Therefore, an increased awareness on the part of the treating physician, as well as of the subject during this time period, is of paramount importance.
Swallowing difficulties (dysphagia)	Swallowing difficulties have been reported following injection to sites other than the injected muscles. Swallowing difficulties may persist for several months, and people who cannot swallow well may need a feeding tube to receive food and water. If	The recommended dosage of Botulinum toxin should not be exceeded. Instructions given in the SmPC regarding application techniques should be carefully observed. Usually, undesirable effects are reported within the first week

Risk	What is known	Preventability
	swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving Botulinum toxin have the highest risk of experiencing these problems.	after treatment. Therefore, an increased awareness on the part of the treating physician, as well as of the subject during this time period, is of paramount importance. The injection of Bocouture is not recommended for patients with a history of dysphagia. These precautionary statements are referred to in the SmPC.
Hypersensitivity	Hypersensitivity reactions have been reported with Botulinum toxin products including severe allergic reactions, hives (urticaria), swelling of soft tissue, and shortness of breath. If serious and/or immediate hypersensitivity reactions occur further injection of Botulinum toxin should be discontinued and appropriate medical therapy immediately instituted.	Instructions given in the SmPC and the Investigator's Brochure regarding contraindications and possible side effects should be carefully observed. Appropriate medical therapy should be available if anaphylactic and/or immediate hypersensitivity reactions occur. Subjects should contact medical aid immediately if experiencing difficulty with breathing, swallowing or speaking due to the swelling of the face, lips mouth or throat, hives, swelling of hand, feet or ankles. These precautions are explicitly referred to in the SmPC resp. in the package leaflet.
Formation of antibodies	Risk factors for antibody-induced therapy failure include the amount of Botulinum toxin applied at each injection series and the interval between injections. Too frequent doses can increase the risk of antibody formation which may lead to treatment failure.	The treatment period between each treatment session should be maintained as referred to in the SmPC.
Worsening of pre-existing neuromuscular disease	Botulinum toxin stops muscle contractions by blocking a normal nerve-ending response without interfering with the muscles or the nerve itself. The neuromuscular disease *amyotrophic lateral sclerosis* is a debilitating disease characterized by rapidly progressive muscle weakness which may be increased by Botulinum toxin.	Subjects with general disorders of muscle activity (e.g. Lambert Eaton Syndrome, Myasthenia gravis) should be excluded from the treatment. Subjects suffering from Amyotrophic lateral sclerosis or other diseases which result in peripheral neuromuscular disorder should be treated with caution and have to be monitored very closely when administered

Risk	What is known	Preventability
		Botulinum toxin. These conditions are explicitly referred to in the SmPC.

Important potential risks

Xeomin

Risk	What is known (Including reason why it is considered a potential risk)
None	
Bocouture	
Risk	**What is known (Including reason why it is considered a potential risk)**
None	

Missing information

Xeomin	
Risk	**What is known**
Use in children	PIPs have been agreed with the European Medicines Agency (EMA). Three studies are investigating the treatment of upper and lower limb spasticity in children and adolescents aged 2 to less than 18 years of age. One additional clinical study is conducted in children from 2 years to less than 18 years of age with chronic sialorrhoea associated with neurologic conditions and/or intellectual disability.
Use in pregnant/lactating women	Seventeen reports of drug exposure to Xeomin/Bocouture before or during pregnancy were received from clinical trials with birth of eleven healthy babies. It is not known whether Botulinum neurotoxin type A is excreted into breast milk.
Bocouture	
Risk	**What is known**
Use in children	A waiver for 'muscle-induced wrinkles' was granted by the EMA with their PIP Decision P/0042/2012. Etiology of the indication upper facial lines including glabellar frown lines, lateral periorbital lines, and horizontal forehead lines is subsumed under the condition 'muscle-induced wrinkles'.
Use in pregnant/lactating women	Seventeen reports of drug exposure to Xeomin/Bocouture before or during pregnancy were received from clinical trials with birth of eleven healthy babies. It is not known whether Botulinum neurotoxin type A is excreted into breast milk.

VI.2.5 Summary of additional risk minimisation measures by safety concern

Xeomin

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

Botulinum toxin effects may, in some cases, be observed beyond the site of local injection (distant or local toxin spread)

Risk minimisation measure(s): Healthcare Professional and patient education
Objective and rationale: To ensure that physicians using Botulinum neurotoxin type A for any approved indication are properly trained and know how to apply the product and how to detect symptoms of local or systemic toxin spread. To ensure that all patients are informed about how to detect symptoms of local or systemic toxin spread and what to do about such symptoms
Main additional risk minimisation measures • Healthcare Professional educational materials to be provided to treating physicians and including advice on: use of an appropriate injection technique, appropriate dose and injection interval, consistent observation of risk factors for toxin spread reactions and caution in the presence of risk factors, use of the correct bioequivalent dose when switching from one Botulinum toxin drug to another, and a thorough discussion with patients on benefit/risk and awareness of the educational material for patients. • The patient information sheet will help the patient to early recognize symptoms that could indicate adverse toxin spread reactions after injection and will further contain the advice to seek speedy medical attention if such symptoms occur.

Swallowing difficulties (dysphagia)

Risk minimisation measure(s): Healthcare Professional and patient education
Objective and rationale: To ensure that physicians using Botulinum neurotoxin A for any approved indication are properly trained and know how to apply the product and how to detect symptoms of local or systemic toxin spread. To ensure that all patients are informed about how to detect symptoms of local or systemic toxin spread and what to do about such symptoms
Main additional risk minimisation measures • Healthcare Professional educational materials to be provided to treating physicians and including advice on: use of an appropriate injection technique, appropriate dose and injection interval, consistent observation of risk factors for toxin spread reactions and caution in the presence of risk factors, use of the correct bioequivalent dose when switching from one Botulinum toxin drug to another, and a thorough discussion with patients on benefit/risk and awareness of the educational material for patients. • The patient information sheet will help the patient to early recognize symptoms that could indicate adverse toxin spread reactions after injection and will further contain the advice to seek speedy medical attention if such symptoms occur.

Hypersensitivity

Risk minimisation measure(s). Additional risk minimisation activity not applicable
Objective and rationale: not applicable
Main additional risk minimisation measures: not applicable

Formation of antibodies

Risk minimisation measure(s) : Additional risk minimisation activity not applicable
Objective and rationale: not applicable
Main additional risk minimisation measures: not applicable

Worsening of neuromuscular disease

Risk minimisation measure(s) : Additional risk minimisation activity not applicable
Objective and rationale: not applicable
Main additional risk minimisation measures: not applicable

Bocouture

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

Botulinum toxin effects may, in some cases, be observed beyond the site of local injection (distant or local toxin spread)

Risk minimisation measure(s): Healthcare Professional and patient education
Objective and rationale: To ensure that physicians using Botulinum neurotoxin type A for any approved indication are properly trained and know how to apply the product and how to detect symptoms of local or systemic toxin spread. To ensure that all patients are informed about how to detect symptoms of local or systemic toxin spread and what to do about such symptoms
Main additional risk minimisation measures • Healthcare Professional educational materials to be provided to treating physicians and including advice on: use of an appropriate injection technique, appropriate dose and injection interval, consistent observation of risk factors for toxin spread reactions and caution in the presence of risk factors, use of the correct bioequivalent dose when switching from one Botulinum toxin drug to another, and a thorough discussion with patients on benefit/risk and awareness of the educational material for patients. • The patient information sheet will help the patient to early recognize symptoms that could indicate adverse toxin spread reactions after injection and will further contain the advice to seek speedy medical attention if such symptoms occur.

Swallowing difficulties (dysphagia)

Risk minimisation measure(s): Healthcare Professional and patient education
Objective and rationale: To ensure that physicians using Botulinum neurotoxin A for any approved indication are properly trained and know how to apply the product and how to detect symptoms of local or systemic toxin spread. To ensure that all patients are informed about how to detect symptoms of local or systemic toxin spread and what to do about such symptoms
Main additional risk minimisation measures • Healthcare Professional educational materials to be provided to treating physicians and including advice on: use of an appropriate injection technique, appropriate dose and injection interval, consistent observation of risk factors for toxin spread reactions and caution in the presence of risk factors, use of the correct bioequivalent dose when switching from one Botulinum toxin drug to another, and a thorough discussion with patients on benefit/risk and awareness of the educational material for patients. • The patient information sheet will help the patient to early recognize symptoms that could indicate adverse toxin spread reactions after injection and will further contain the advice to seek speedy medical attention if such symptoms occur.

Hypersensitivity

Risk minimisation measure(s). Additional risk minimisation activity not applicable
Objective and rationale: not applicable
Main additional risk minimisation measures: not applicable

Formation of antibodies

Risk minimisation measure(s) : Additional risk minimisation activity not applicable
Objective and rationale: not applicable
Main additional risk minimisation measures: not applicable

Worsening of neuromuscular disease

Risk minimisation measure(s) : Additional risk minimisation activity not applicable
Objective and rationale: not applicable
Main additional risk minimisation measures: not applicable

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Xeomin

Study/activity	**Objectives**	**Safety concerns**	**Status**	**Planned date for**

(including study number)		**/efficacy issue addressed**		**submission of (interim and) final results**
None				
Bocouture				
Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
None				

Studies which are a condition of the marketing authorisation

Xeomin: None

Bocouture: None

VI.2.7 Summary of changes to the Risk Management Plan over time

Table 21: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
5.1	07.10.2010	The MAH has identified the following risks that require further evaluation additional to the risk "distant or local toxin spread": Dysphagia (in previous RMPs dysphagia was presented as part of distant or local toxin spread), formation of antibodies, hypersensitivity, patients with pre-existing neuromuscular diseases	Update requested by the RMS (Germany) during the variation application procedure DE/H/2619/001/IB/001 for Bocouture
6.0	07.02.2012	No new safety concerns	Update due to the new indication for Bocouture [lateral periorbital lines (crow's feet lines)] Additional repeated dose data and new literature data has been included
7.0	07.04.2014	No new safety concerns	Update according to new RMP Guidelines (GVP Module V)

8.0	28.07.2014	No new safety concerns	Additional study data has been included, approval status has been updated
9.0	27.02.2015	No new safety concerns	Update due to the new indication for Bocouture (upper facial lines) Additional study data has been included, approval status has been updated
10.0	31.07.2015	No new safety concern	Update according to authority request and to reflect currently approved SmPC
10.1	25.11.2015	No new safety concern	Update according to authority request
10.2	16.02.2016	No new safety concern	Update according to authority request
10.3	09.03.2016	No new safety concern	Update according to authority request