1.8.2 Risk Management Plan

Active substance(s) (INN or common name):	Xeomin: Clostridium Botulinum neurotoxin type A (150 kD), free from complexing proteins Bocouture: Botulinum toxin type A (150 kD), free from complexing proteins (an INN for the drug substance has not been assigned) (Company code used: NT 101)
Pharmaco-therapeutic group (ATC Code):	Muscle relaxant, peripherally acting agent (M03AX01)
Name of Marketing Authorisation Holder or Applicant:	Merz Pharmaceuticals GmbH
Number of medicinal products to which this RMP refers:	One
Product(s) concerned [brand name(s)]:	Xeomin® Bocouture®

Data lock point for this RMP	15-Apr-2013	Version number	7.0
Date of final sign off	07-Apr-2014		

VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

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. For glabellar frown lines and lateral periorbital lines no data is published.

VI.2.2 Summary of treatment benefits

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 dystonias. In controlled studies it has been shown to markedly improved 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, 279 subjects have been treated with repeated dose. Statistically significant and clinically meaningful benefit compared to placebo was observed. The therapeutic effect is a localized muscle weakness with potential side effects not affecting the whole body.

NT 201 has been granted marketing authorization in 13 countries in the European Economic Area and in nine other countries for the treatment of several disorders of the nervous system including cervical dystonia. NT 201 is marketed under the trade name Xeomin for treatment of cervical dystonia. The first marketing authorization 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 600.000 persons in studies and in the market.

Blepharospasm

Blepharospasm is a progressive disease characterized 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, 98 subjects have been treated with repeated dose. Statistically significant and clinically meaningful benefit compared to placebo was observed. The therapeutic effect is a localized muscle weakness with potential side effects not affecting the whole body.

NT 201 has been granted marketing authorization in 13 countries in the European Economic Area and in nine other countries for the treatment of several disorders of the nervous system including blepharospasm. NT 201 is marketed under the trade name Xeomin for treatment of blepharospasm. 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, Xeomin has so far been received by nearly 600,000 people in studies and in the market.

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, 265 subjects have been treated with single dose treatment of NT 201 and 75 with placebo during clinical trials, 136 subjects have been treated with repeated dose. Response rates of more than 60% were observed with NT 201. The therapeutic effect is a localized muscle weakness with potential side effects not affecting the whole body.

NT 201 has been granted marketing authorization in 13 countries in the European Economic Area and in nine other countries for the treatment of several disorders of the nervous system including upper limb spasticity. NT 201 is marketed under the trade name Xeomin for treatment of spasticity. The first marketing authorization 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, Xeomin has so far been received by nearly 600,000 people in studies and in the market.

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 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, 800 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.

NT 201 has been marketed since 15 Sep 2009 in Germany for glabellar frown lines under the trade name Bocouture. Since this date, Bocouture has so far been received by nearly 200,000 people in studies and in the market.

Lateral periorbital lines (crow`s feet)

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). No BTX-A preparations has yet been approved for the therapy of lateral periorbital lines in the European Economic Area. 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 30 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.

VI.2.3 Unknowns relating to treatment benefits

In the clinical studies most patients were white Caucasians with a mean age of 51 years (cervical dystonia), 62 years (blepharospasm), 58 years (spasticity), 45 years (glabellar frown lines) and 47 years (lateral periorbital lines) with an age range from 18 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

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 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 swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving Botulinum	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 im-

Risk	What is known	Preventability
	toxin have the highest risk of experiencing these problems.	portance Subjects who already had swallowing difficulties or breathing problems before should be treated with extreme caution. This precaution is explicitly 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 Investigators Brochure regarding contraindications and possible side effects should be carefully observed. Adrenaline and other medical aids for treating anaphylaxis should be available during each therapy session. Subjects should contact medical aid immediately if experiencing hives, swelling, wheezing, feeling faint, and shortness of breath. 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 dosing of Botulinum toxin may result in antibody formation which may lead to treatment resistance.	The treatment period between each treatment session should be maintained as referred in the SmPC.
Patients with 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 Botulinum toxin. These conditions are explicitly referred to in the SmPC.

Important potential risks

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

Important missing information

Risk	What is known
None	

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

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

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

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 recognise 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.

Dysphagia (swallowing difficulties)

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 recognise 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 minimization 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

Patients with 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

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

None

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

Table 1: 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 proposed for Bocouture [lateral periorbital lines (crow's feet)] 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)