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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
Ach	Acetylcholine
ADQ	Abductor digiti quinti
AE	Adverse Event
AESI	Adverse event of special interest
AH	Abductor hallucis
ANCOVA	Analysis of covariance
AR	Adverse reaction
AUEC	Area under the effect (area of anhidrosis) curve
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BLEPH	Blepharospasm
BoNT/A	Botulinum neurotoxin type A (NT201, Xeomin, Bocouture, Xeomeen)
BSDI	Blepharospasm disability index
BTX-A	Botulinum toxin type A
BTXCo	Clostridium botulinum toxin type A [900 kDa] (Botox, Vistabel)
CAmR	CMAP amplitude M-wave reduction
CD	Cervical dystonia
CETS	Composite endpoint treatment success
CF	Crow's feet
CI	Confidence interval
CMI	Consumer Medicine Information
CMAP	Compound muscle action potential
CNS	Central nervous system
CSR	Clinical study report
CTD	Common technical document

Abbreviation	Meaning
ECG	Electrocardiogram
EDB	Extensor digitorum brevis (muscle)
EEA	European Economic Area
ELISA	Enzyme linked immunosorbent assay
EMG	Electromyography
EU	European Union
FAS	Full analysis set (for efficacy analyses)
FDA	Food and Drug Administration
FIA-AB	Fluorescence immunoassay for antibodies
FWS	Facial Wrinkle Scale
GCP	Good Clinical Practice
GFL	Glabellar frown lines
GLP	Good laboratory practice
GMP	Good Manufacturing Practice
HSA	Human serum albumin
HV	Healthy volunteer
ICH	International conference on harmonisation
IM	Intramuscular
ISS	Integrated summary of safety
ITT	Intent to treat
JRS	Jankovic rating scale
kDa	KiloDalton
LD ₅₀	Lethal dose, 50%
MU	Mouse LD50 Units (median lethal intraperitoneal dose)
mV	Millivolt
NT 201	Botulinum neurotoxin type A free from complexing proteins (Xeomin,

Abbreviation	Meaning
	Bocouture, Xeomeen)
NOAEL	No observable adverse effect level
OLEX	Open label extension (period)
PD	pharmacodynamic
PI	Product Information
PK	Pharmacokinetic
PPS	Per protocol set (for efficacy analyses)
PSUR	Periodic safety update report
PT	Preferred term
RR	Resting rate
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of product characteristics
SNAP	Synaptosomal associated protein
SNAP-25	Synaptosome associated protein of 25,000 daltons
SOC	System organ class
SP	Spasticity
TEAE	Treatment emergent adverse event
TGO	Therapeutic Goods Order
TPP	Treated perprotocol
TWSTRS	Toronto Western Spasmodic Torticollis Rating Scale
U	Units
UK	United Kingdom
USA	United States of America
USAN	United States adopted name
VAMP	Vesicle associated membrane protein

Abbreviation	Meaning
PR	PR interval
QT	QT interval
QTc	Corrected QT interval
QRS	QRS complex
CNS	Central nervous system
MW	Molecular weight
IV	intravenous
GD	Gestational day
IP	Intraperitoneal
PO	oral
CER	Clinical evaluation report
RMP	Risk management plan
MP	Main Period

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	17 March 2014
<i>Active ingredient:</i>	Botulinum toxin type A
<i>Product name:</i>	Xeomin
<i>Sponsor's name and address:</i>	Merz Australia Pty Ltd Level 3, 244 Coward St, Mascot, 2020 NSW
<i>Dose form:</i>	Powder for injection
<i>Strength:</i>	50 and 100 LD50 units
<i>Container:</i>	Glass vial
<i>Pack size(s):</i>	1 vial
<i>Approved therapeutic use:</i>	<ul style="list-style-type: none">• Cervical dystonia in adults• Blepharospasm in adults• Post-stroke spasticity of the upper limb in adults• Glabellar frown lines in adults
<i>Route of administration:</i>	Injection
<i>Dosage:</i>	The dosage of Xeomin will be individualised according to indication and individual patient.
<i>ARTG number (s):</i>	205507 and 205508

Product background

This AusPAR describes the application by the sponsor to register Xeomin for the following indication;

- *Cervical dystonia in adults*
- *Blepharospasm in adults*
- *Post-stroke spasticity of the upper limb in adults*
- *Glabellar frown lines in adults*

Xeomin is a highly purified, freeze-dried formulation of Botulinum neurotoxin type A.

Xeomin is synthesized as a single chain polypeptide with a molecular weight of approximately 150 kDa, using a wild type strain of the anaerobic bacterium *Clostridium botulinum*. The neurotoxin is produced as part of a high molecular weight complex (approximately 900 kDa) consisting of at least 5 additional proteins (complexing proteins). During the manufacturing process of the drug substance, the neurotoxin, is separated from the complexing proteins. The active ingredient thus represents the pure neurotoxin type A.

Xeomin was anticipated to be less immunogenic than available Botulinum products due to the absence of complexing proteins.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 21 March 2014.

At the time the TGA considered this application, similar applications had been approved in the United States (US), Canada and the European Union (EU), and was first marketed in July 2005 in Germany. Both proposed strengths are not approved in all countries. Botox and Dysport are registered products containing Botulinum toxin type A. Additional products are marketed in other countries.

Product Information

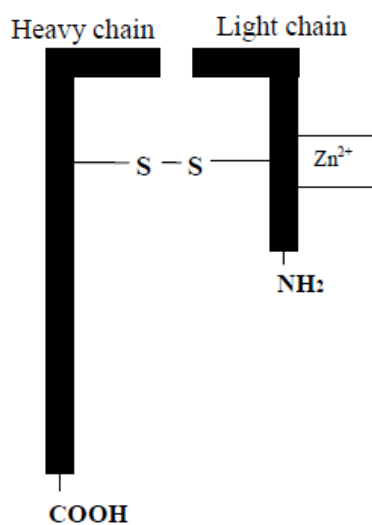
The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

II. Quality findings

Drug substance (active ingredient)

Structure

The NT 101 drug substance is synthesized by *Clostridium botulinum* type A as a single chain protein (1,296 amino acid residues molecular weight approximately 150 kDa), which is subsequently split between residues 438 and 439 as well as between residues 448 and 449 by an endogenous protease during post-translational modification. A decapeptide (residue 439 to residue 448) is cleaved from the protein, resulting in a heavy chain, with a molecular weight of approximately 100 kDa, and a light chain, with a molecular weight of approximately 50 kDa. These separate chains are covalently linked via a single disulphide bond (Figure 1). The light chain is associated with one atom of zinc and functions as a zinc-dependent endopeptidase. The heavy chain comprises two functional domains: the N-terminal section is the translocation domain and the C-terminal section is the binding domain.

Figure 1. Structure of NT 101

Cell banking processes are satisfactory. All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Physical and chemical properties

The drug substance is clear colourless solution that consists of single, heavy and light chain proteins. The minor protein bands are considered as product-related impurities.

The company has listed all routine tests performed to control the physicochemical and biological quality of the NT 101 drug substance. The biological activity of Botulinum toxin type A is measured by an in vivo mouse LD₅₀ assay against the in-house reference standard. The assigned biological activity for the current reference standard (information redacted) is 100.691 LD₅₀ units/vial. The LD₅₀ units estimated by this assay provide the basis for formulation of the drug product.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use have had appropriate validation data submitted in support of the test procedures.

Stability

Stability data have been generated under real time/stressed conditions to characterise the stability/degradation profile of the substance and to establish a shelf life. The real time data submitted support a shelf life of 36 months at -80°C.

Drug product (DP)

Formulation(s)

NT 201 drug product is supplied as a powder for solution for injection (lyophilisate) packed in glass vials. The vials are closed with rubber stoppers and aluminium caps. NT 201 is reconstituted with commercially available 0.9 % physiological saline which is not supplied in the pack.

Each vial contains either 50 or 100 mouse LD₅₀ units of Clostridium botulinum type A toxin (150 kD), free from complexing proteins, 4.7 mg of sucrose and 1.0 mg of human serum albumin (HSA). The formulation for the 50 U/vial is exactly the same as for 100 LD₅₀ Units/Vial except for the amount of toxin, which has been reduced by half in the lower dosage strength. The lower neurotoxin amount in the NT 201-50 Units presentation is achieved by keeping the filling amount per vial (0.5 mL for both presentations prior to lyophilisation) and the concentration of the excipients in the formulated bulk solution constant but to halve twice as large batch volume for the 50 unit presentation than that for the 100 Unit presentation.

Due to differences in the potency assay, Xeomin unit is specific to Xeomin, and therefore one unit of Xeomin is not equivalent to one unit of other preparations of Botulinum toxin.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product have been submitted to TGA.

The release specifications are similar for both DP presentations except for residual moisture, Clostridium botulinum Neurotoxin Type A concentration, sucrose content and biological activity (potency).

Appropriate validation data have been submitted in support of the test procedures.

Stability

Stability data have been generated under real time conditions to characterise the stability profile of the product. The proposed shelf life is 36 months when stored at less than or equal to 25°C. (Please note that the product is acceptable to reach to the temperature of 25°C, although the label indication has been amended to state as 'store below 25°C' to comply with the Therapeutic Goods Order (TGO) 69¹).

In-use stability data have also been submitted. The proposed shelf life for the reconstituted product is 24 hours when stored at 2 to 8°C.

Photostability data confirmed that the product is photostable.

Biopharmaceutics

There is no biopharmaceutics data. The company has stated in the Product Information (PI) that classic kinetic and distribution studies cannot be conducted because the active substance, botulinum neurotoxin type A is applied in such small quantities (pictograms per injection) and it binds so rapidly and irreversibly to cholinergic nerve terminals.

Labelling, packaging and documentation

The initially identified deficiencies were that the Carton label, PI, and Consumer Medicine Information (CMI) contained no complying storage condition and excipients with TGO 69, the potency expression (LD₅₀ units) is not product specific, and few other minor issues. The company was asked to provide updated labelling documentation complying with TGA 69 and product specific expression of the LD₅₀ units. Revised labelling was provided. While the revised labels are appropriately updated, the ABN committee has decided to

¹ Therapeutic Goods Order No. 69 - General requirements for labels for medicines (27/08/2001).

adopt the ingredient name 'incobotulinumtoxinA' for Botulinum toxin type A. The company was contacted to negotiate the naming update to comply with TGO 69.

All label issues have been resolved and the Quality aspects of the PI/CMI are satisfactory.

Good Manufacturing Practice (GMP)

All manufacturing sites have current GMP clearance certificates except for two. The company was asked to provide the GMP certifications for these sites, and their responses of 2 October 2013 and 28 October 2013 indicate that they have submitted the appropriate applications. There is no reason to expect that the applications for clearance updates will not be completed by the time of registration.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The following outstanding issues remain:

- GMP clearances for two of the manufacturing sites remain outstanding.

There is no reason to expect that the applications for clearance updates will not be completed by the time of registration.

There are no further Quality Objections to the registration of this product.

III. Nonclinical findings

Introduction

Xeomin (NT 201) is a Botulinum toxin type A (BoNT/A) muscle paralytic agent belonging to a well-established class of drugs, which has been purified to remove the clostridial complexing proteins that are present in the previously approved products Botox and Dysport. The in vivo primary pharmacology data were consistent with NT 201 producing a long lasting blockade of acetylcholine release at cholinergic nerve terminals and/or the neuromuscular junction. The muscle paralytic effects of NT 201 appear to be comparable to those of Botox, and a full functional recovery was observed.

The potency of BoNT/A is measured in units (LDU), corresponding to the median lethal dose (LD50) in mice after an IP injection (these potency units are not interchangeable with those of other commercial preparations of botulinum toxin).

Doses per injection range from a low dose of 30 LDU for the treatment of glabellar frown lines to the maximum clinical recommended dose of up to 400 LDU per treatment of spasticity (8 LDU/kg for a 50 kg human).

Reduced muscle tension lasts about 3 months. Treatment is repeated indefinitely after muscle function has recovered. The clinical dosing regimen includes dosing intervals of 6 weeks and 3 to 4 months.

NT 201 (Xeomin) is fermentation-derived BoNT/A which has been highly purified to remove the clostridial non-toxin complexing proteins (haemagglutinin and non-haemagglutinin proteins that do not contribute to the therapeutic paralytic effect). This is

in contrast to other already approved products such as Botox (Allergan) or Dysport (Ipsen), which contain these complexing proteins.

Foreign protein content is a known factor for secondary therapy failure during clinical use due to the formation of neutralising antibodies. On this basis, the sponsor proposes that the potential clinical risk of antibody formation with long-term use of NT 201 is lower and the incidence of treatment failures is expected to be reduced.

However, the nonclinical information regarding the immunogenicity potential of Xeomin is scant (that is, potential of Xeomin to generate neutralizing antibodies) as only two antigenicity studies were submitted (in rabbits) after repeated intradermal (intracutaneous) dosing.

BoNT/A has been in clinical use for a number of years, and its pharmacology is well known. The submitted data were in accordance with the International conference on harmonisation (ICH) guideline² on the 'nonclinical safety evaluation of biotechnology-derived pharmaceuticals'; this is acceptable as BoNT/A is a biotechnology derived pharmaceutical, originating from live bacteria. The data consisted of well-designed and reported studies that were conducted in compliance with Good Laboratory Practice (GLP) requirements when required (that is, with the exception of dose finding studies for reproductive toxicity testing in non-pregnant rabbits, pregnant rats or juvenile rats). The dossier also contained published literature reports (non-GLP) submitted in support of certain parts of the application (for example, distribution).

Sponsor submitted studies with NT 201 and/or NT 101 were designed based on the proposed clinical dose, dosing regimen and duration; the maximum clinical dose is 400 LDU per administration (8 LDU/kg for a 50 kg patient). The clinical route of administration is intramuscular (IM) and the clinical dosing regimen includes dosing intervals mostly of 3 to 6 months (as the effects of each treatment generally lasts 3 to 4 months); however, it may last significantly longer or shorter as outlined in the draft Product Information document. In the case of the cervical dystonia, 300 LDU (equivalent to 6 LDU/kg for a 50 kg patient) is indicated for injection into various muscles over a more frequent interval of 6 weeks (treatment is repeated indefinitely after muscle function has recovered).

The package of studies was generally adequate in scope to assess the safety and toxicity profile of Xeomin and to assess possible differences in potency or toxicity with previously approved.

Pharmacology

Primary pharmacology

The mechanism of action of the BoNT/A class of muscle relaxant drugs is well established.

NT 201 (which contains BoNT/A as the active ingredient) acts on the neuromuscular junction and muscles where chemical muscle denervation results in blockade of acetylcholine release, thus reducing muscle tension and functionally denervating (inactivating) muscle endplates and muscle spindles for a long duration. Functional recovery after injection normally takes place after many weeks as nerve terminals sprout and reconnect with the endplate.

Typically, exposure to BoNT/A agents is assessed by examining the paralytic activity of the drug or other biological activity (EMG amplitude). Three in vivo studies submitted by the

² ICH S6: Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals; CPMP/ICH/302/95).

sponsor confirmed the therapeutic target of NT 201 is the neuromuscular junction and muscles, producing the desired effect of reducing muscle tension and paralysis within hours to days of local intramuscular (IM) injections.

The paralytic effect of NT 201, Botox and Dysport was assessed in the regional paralysis test after repeated IM injections in the gastrocnemius muscle in mice. The time to onset, degree and/or duration of paralysis were dose-dependent, with increased severity after the 2nd or 3rd dose and complete paralysis seen 3 to 4 days after the initial dose. Muscular atrophy (and reduced treated leg diameter) was seen after the second injection.

No adverse clinical signs were evident except for transient dose-dependent decreases in body weight after each injection (starting 3 days after the first injection).

Overall there were only minor differences between NT 201 and Botox in the paralytic effect following dosing of equivalent LD50 (mouse) units. Botox, Dysport and NT 201 showed similar time to onset of paralysis and dose-response profiles, and similar body weight changes were observed for NT201 and Botox in all three dose cycles.

The paralytic efficacy of single IM doses of NT 201 and Botox in conscious, non-restrained male Cynomolgus monkeys, showed that at 22 hours post injection the injected gluteus medius muscle activity markedly decreased, with the greatest paralytic effect seen 1 to 2 weeks after injections. Recovery of muscle activity started about 9 weeks post injection; after 37 weeks the muscle function had fully recovered. Overall, the time-course of paralysis and the paralytic activity of NT 201 and Botox in monkeys were similar following single intramuscular injections of 16 LDU/kg.

Recovery of NT 201 denervated muscle

The time course of re-innervation and recovery of muscle function was investigated following repeated IM injections of NT201 into the gastrocnemius muscle in rats (10 times weekly IM injections at 2, 8 or 16 LDU/kg). Immunohistochemical staining for surrogate markers of denervation was positive 1 week after the last injection, but not after 26 weeks. Full recovery of muscle function was generally observed after 26 weeks, although at the lower doses of 2 or 8 LDU/kg functional recovery occurred more rapidly. Muscle function had fully recovered after 26 weeks, although histological correlates (muscle atrophy) showed only partial recovery at this time. In this study, NT201 produced the expected atrophy of injected muscles at all dose-levels, which led to limping and signs of paralysis; it also induced swelling of the abdomen at 8 and 16 LDU/kg.

The primary pharmacology data support the proposed therapeutic use of NT201. The data confirm NT 201's activity at the mechanistic level both in terms of muscle paralytic activity in mice and monkeys and aspects of its 'chemical' muscle denervation in rats. The findings reflect the expected effects of the known pharmacological activity of Botulinum toxin type A, including atrophy of the treated muscles accompanied by impaired mobility and reduced body weight gain. The muscle paralysis effects in mice and monkeys following IM injections of NT 201 and Botox were comparable. The time course of onset and recovery, maximal paralytic effects and clinical signs of toxicity were comparable to those observed with Botox and Dysport, confirming that the clostridial non-toxin complexing proteins play no role in the pharmacological activity of the toxin.

Secondary pharmacology

This was addressed indirectly in the acute toxicity data (see below).

The applicant acknowledged that BoNT/A induced blockade of acetylcholine release can potentially occur at all cholinergically innervated autonomic nervous system sites, including preganglionic nerve terminals, parasympathetic postganglionic nerve terminals, sympathetic postganglionic nerve terminals on sweat glands and on sympathetic vasodilator nerve terminals on blood vessels in skeletal muscle. Potential targets include

the eye, cardiovascular system, respiratory and gastrointestinal tract and smooth muscle of the urinary and biliary tract and uterus. According to the applicant, unwanted autonomic effects are occasionally reported after therapeutic BoNT/A use.

Based on the data submitted, Xeomin does not appear to pose any additional risk compared with previously approved BoNT/A products.

Safety pharmacology

Specialised safety pharmacology studies were restricted to the cardiovascular system (in vitro hERG assay and electrocardiography (ECG) parameters in monkeys), central nervous system (CNS) (locomotor activity in mice) and gastrointestinal (GI) tract (charcoal meal transit in rats).

Not all of the safety pharmacology studies were Good Laboratory Practice (GLP) compliant (hERG assay) but the design and conduct of the studies were adequate to reveal any treatment-related effects. Some studies also included a comparison of NT 201 with Botox and/or Dysport. In the submitted studies, adverse findings of mortality in mice or paralysis of the gluteus muscle in monkeys was attributed to the known pharmacological activity of Botulinum toxin type A.

However, there appears to be very limited nonclinical information regarding the effects of NT 201 on respiratory parameters, assessed in either dedicated safety pharmacology studies or as part of acute/repeat dose toxicity studies. Comparative assessment studies with other BoNT/A products would have been useful in this regard; refer also to Assessment, Acute Toxicity for a discussion that the critical target in lethal BoNT/A poisoning is probably the respiratory musculature (that is, lethality observed in the single dose toxicity studies is likely an effect of NT 201 on respiratory muscles).

Overall, there were no differences between NT 201, Botox or Dysport on locomotor activity (static and active movements) assessed within an acute IV toxicity study in mice at doses up to 68 LDU/kg with similar dose-dependent decreases in mobility observed for NT 201, Botox and Dysport starting at 20 LDU/kg (48 to 72 h post dose). At greater than or equal to 30 LDU/kg, a significant dose-dependent decrease in static and active movements (compared to controls) was already seen 24 h post dose. The no observed adverse effect level (NOAEL) was 9 LDU/kg, which corresponds to a blood concentration of 0.121 LDU/mL assuming a blood volume in this species of 74.5 mL/kg³. This concentration is comparable to the maximum anticipated human blood concentration of 0.123 LDU/mL (assuming accidental IV injection of the maximum clinical single dose of 400 LDU and a human female blood volume of 65 mL/kg⁴). NT 201 also had no effect on intestinal transit of a charcoal meal in the conscious rat 4 days after a single IM injection of 8, 16 or 32 LDU/kg; paralysis of the injected limb was confirmed in all dosed animals. The NOAEL was 32 LDU/kg, which is 4 times the maximum therapeutic dose of 8 LDU/kg.

At a concentration of 10,000 LDU/mL, NT 101 had no effect on hERG tail currents at –20 mV in Chinese hamster ovary (CHO) cells stably expressing hERG channels using patch clamp recordings. This concentration exceeds the maximum anticipated concentration in human blood (assuming accidental vascular injection, as discussed above) by more than 80 000 fold. An interaction of NT 101 with hERG channels is unlikely.

A cardiovascular safety study examined electrocardiogram (ECG) parameters in monkeys (Study 442/015) for 9 weeks, following a single IM injection of 16 LDU/kg (this dose corresponds to the high dose in the 13 week repeat dose toxicity study, 442/016). One

³ Mitruka, B.M. & Rawnsley, H.M., Clinical Biochemical and Haematological Reference Values in Normal Experimental Animals, Masson Publishing, NY, 1977, cited in: CRC Handbook of Toxicology, Ed. M. J. Derelanko & M. A. Hollinger, CRC Press, 1995.

⁴ The sponsor's Nonclinical Overview.

week after treatment with NT 201 or Botox, paralysis of the injected gluteus muscle was observed and was associated with a heart rate increase for both agents, with corresponding effects on the R wave to R wave interval (RR) and Q-T interval. However, this effect was not considered to be treatment related, and was likely due to locomotor stress resulting from muscle paralysis. There was also a slight decrease in heart rate (bradycardia) 2 to 3 hours post dose for both agents, accompanied by an increase in resting rate (RR) interval which was likely related to administration of NT 201 under slight ketamine anaesthesia. From week 4, ECG parameters returned to baseline. Overall, NT 201 had no overall adverse effects on ECG parameters. The NOAEL for NT 201 was 16 LDU/kg (twice the maximum recommended clinical dose of 8 LDU/kg).

ECG and cardiovascular examinations were also conducted in all the repeat dose toxicity studies in monkeys with no NT 201 treatment related effects observed on blood pressure, heart rate or ECG parameters (PR interval (PR), QT interval (QT), corrected QT interval (QTc), QRS complex (QRS)). Doses of up to 16 LDU/kg, administered at a minimum of 4 weekly intervals, were associated with exposures of up to 4 fold the maximum therapeutic dose. This exposure ratio is based on normalised data of the total dose administered to monkeys and humans over a 12 week period (monkeys: a total of 48 LDU/kg; humans: 12 LDU/kg (600LDU; or 300 LDU (6 LDU/kg for a 50 kg patient) over a 6 week period for the cervical dystonia indication).

Overall, there are no specific concerns raised from the safety pharmacology studies. Where Botox was used as a comparator (CNS and ECG parameters in monkeys), the pharmacological effects of NT 201 and Botox were comparable.

Pharmacokinetics

Pharmacokinetic studies with NT 101/201 cannot be undertaken because it is given in such minute quantities (picograms per injection) and it binds so rapidly and irreversibly to cholinergic nerve terminals. Exposure is instead estimated indirectly by examining its paralytic activity or other biological activity (EMG amplitude). For the same reason, human pharmacokinetic studies with NT 201 have not been conducted. NT 201 is a 150 kDa BoNT/A molecule free of complexing proteins. In contrast, Botox and Dysport consist of the Botulinum neurotoxin type A together with nontoxic complexing proteins that produce conglomerates of 900 kDa (Botox) or 300 to 900 kDa (Dysport). Due to the size of the complexes, diffusion of the neurotoxin into adjacent tissues may be slower with the high molecular weight (MW) complexes compared with the lower MW complexes or with free neurotoxin. The distribution/ potential for spread of NT201 from the injection site at remote sites may differ from those of other Botulinum toxin type A products. Two published studies on this issue were submitted which showed only a marginal local spread of NT 201 or the purified 150 kDa Botulinum toxin from the intramuscular injection site in the surrounding tissue and/or into the contralateral muscles.

Carli et al⁵ compared the diffusion of Botox, Dysport or Xeomin from the site of IM injections in the tibialis anterior muscle of the hindlimb of mice into adjacent (soleus) and distant (gastrocnemius and quadriceps femoris) muscles to determine the extent of BoNT/A diffusion. Expression of the neuronal cell adhesion molecule protein (N CAM, a surrogate marker for denervation of a muscle) was measured by immunohistochemistry or Western blot to determine the effective spread or diffusion of the three BoNT/A products following injection.

N-CAM expression was detected in the injected tibialis anterior muscle for all 3 agents as early as Day 7 (increasing from Days 14 to 21; and starting to decrease at Day 30), but was barely detectable after 60 days, suggesting complete recovery of the muscle. Limited

⁵ Carli L et al. (2008). *Toxicon* 51 Suppl 1, 9.; Carli L et al. (2009). *Muscle and Nerve* 40, 374-80.

diffusion of Xeomin, Botox and Dysport were detected in the adjacent soleus muscles, while only very low levels were seen in the more distant gastrocnemius or quadriceps muscles. There was no N-CAM staining on the contralateral side, indicating there were no distant effects in this study. There were no overall differences in the findings for the three products (which were so similar in their effects as to be indistinguishable), and therefore there were no differences between complexed or free forms with respect to diffusion into adjacent/distant muscles.

In a study using (125I)-labelled purified BoNT/A (150 kDa) or the (125I)-labelled 900 kDa BoNT/A-haemagglutinin complex injected into the gastrocnemius muscle of rats or the eyelids of rabbits⁶, both injections showed similar tissue distributions, with very limited diffusion from the injection sites. Additionally, there were no findings of systemic effects or general toxicity in either rats or rabbits, suggesting both the purified (free from complexing proteins) and the complexed neurotoxin remained at the injection site.

Toxicology

Acute toxicity

GLP single dose and acute toxicity studies with NT 201 (and/or NT 101) of 4 to 14 days duration were conducted in mice (IM, intravenous (IV), intraperitoneal (IP) and oral (PO) dosing routes) and rats (PO; IM (dose range finding study for a safety pharmacology study)). On a weight of evidence basis, the toxicity profile of NT 201 was similar to that of Dysport and/or Botox, which were included in some of the submitted studies. Doses administered by the clinically relevant route (that is, IM) included doses of up to 150 LDU/kg in mice and up to 64 LDU/kg in rats. The submitted mouse studies were designed as LD50 assays to establish unitage (that is, U or LDU values) of the product or to identify and compare lethal doses of NT201 to other Botulinum toxin type A (BoNT/A) products (Dysport and/or Botox). Mortality was observed with all dosing routes (only in mice) and is likely to have occurred following paralysis of the respiratory muscles as result of the pharmacological action of NT 201. Other findings in mice and/or rats of reduced mobility, muscular tone, body weights and ataxia were also related to the pharmacological effects of local muscle paralysis and/or low grade blockade of autonomic neurotransmission (piloerection, ptosis, lacrimation and mydriasis). No unexpected findings were observed in relation to the well-known class effects.

Based on the LD50 in mice, NT 201 was significantly more potent when administered by the IM (41-87 LDU/kg; Botox, 87 LDU/kg), IV (50 LDU/kg; Botox, 50 LDU/kg) or IP (5.37 pg/animal) routes compared with dosing by the PO route (5,000,000 LDU/kg).

Although no unexpected treatment related systemic effects or other specific organ toxicity was reported (that is, effects other than the expected pharmacological effects of muscle paralysis), based on the findings in mice with dosing by the IM route, systemic toxicity following IM administration could theoretically be a potential clinical risk based on low exposure margins compared to the maximum recommended clinical dose. The NOAEL in the mouse for IM dosing was 5 LDU/kg, which is approximately 0.6 times the maximum human therapeutic dose of 8 LDU/kg. However, taking into consideration that NT 201 is a local treatment and that adequate overseas clinical experience with the use of Xeomin is already available, the low exposure margins regarding potential systemic toxicity observed in the nonclinical studies are mitigated to some extent. Additionally, NT 201 showed similar potency to Botox in terms of lethality by the IM and intravenous (IV) routes and consequently, lack of complexing proteins does not appear to influence acute toxicity.

⁶ Tang-Liu DD et al. (2003) *Toxicol* 42, 461-469.

Repeat-dose toxicity

Pivotal GLP repeat dose local (IM) toxicity studies were performed in mice, rabbits and monkeys to characterize the local injection site toxicity following IM injections or the potential toxicity that might result from systemic exposure of NT 201, which is of great concern in humans. The dosing intervals were chosen after taking into consideration the long lasting paralytic effect of NT 201 to establish the maximum feasible exposure. All studies were conducted with the intended clinical route (IM). No toxicokinetic studies accompanied the submitted toxicity studies and given the nature of NT 201, this is considered acceptable (that is, doses are given IM in small volumes to avoid systemic exposure). The duration of the pivotal studies, the species used and group sizes were consistent with ICH guidelines. Comparative toxicity studies with Dysport and/or Botox included the 28 week mouse study and the 13 week monkey study.

Relative exposure

Relative animal/human exposure calculations based on plasma area under the curve (AUC) or maximum concentration (C_{max}) were not possible in the absence of pharmacokinetic/toxicokinetic data for NT 201; thus, comparison of relative exposure in the major nonclinical studies was made based on dose per bodyweight (that is, LDU/kg).

On an ongoing (or repeat dose) basis, the maximum recommended clinical dose of NT 201 is 300 LDU, given every 6 weeks for the cervical dystonia indication (600 LDU in 12 Weeks (12 LDU/kg for a 50 kg patient). This clinical dosing regimen was not used in the animal studies where dosing was more frequent, from daily (Reproductive Toxicity studies) to every 12 weeks (Repeat Dose Toxicity studies) depending on the study type, which would possibly result in repeated (and thus greater overall) exposure to NT 201. To account for the difference in dosing frequencies, this could be overcome by normalisation of all doses (nonclinical and clinical) to an equivalent common dosing interval (for example, weekly, monthly) and comparing doses over identical time periods (for example, 14 days for the rat embryofeotal development study). Comparison (normalisation) of total exposure in a 12-week period (total animal dose versus total human dose) achieves the same result (see Table 2 below and in Reproductive Toxicity section).

Although the doses in the nonclinical toxicity studies did not represent several multiples of the proposed clinical dose, they are considered to be appropriate, with dosing limited by systemic toxicity and/or local toxicity in the pivotal repeat-dose toxicity studies. Estimation of exposure multiples in the pivotal monkey toxicity studies based on dose per bodyweight (that is, LDU/kg) demonstrated low (1 to 4 fold) exposure multiples compared with the clinical use of NT 201. It is acknowledged that NT 201 is essentially a local treatment and therefore, despite the evidence of some systemic toxicity in animal studies, the above considerations regarding relative doses per bodyweight (that is, LDU/kg) contain a degree of uncertainty. Definitive NOAELs were not established in the pivotal repeat dose toxicity studies.

Exposure comparisons were also calculated based on dose per body surface area (BSA, that is, LDU/m²). These calculations may not be appropriate considering the disposition and metabolism of NT 201, but they were included for completeness. The exposure margins as quoted in Product Information documents are historically based on comparisons on a dose per body weight basis (that is, LDU/kg).

Table 2. NT 201 exposure calculations (Total Dose: (LDU/kg) or (U/m²)) in repeat dose toxicity studies

Study no.	Species (Route)	NT 201 Dose (U/kg) ^a (Frequency)	12 Weeks Total dose (LDU/kg)	Dose multiples (based on total dose (LDU/kg) in 12 weeks)	12 Weeks Total dose (LDU/m ²) ^b	Dose multiples (based on total dose (LDU/m ²) in 12 weeks)
11125/1/98	Mouse IM	13, 16.5, 20.5, 25.5, 32 LDU/kg Dosing: 19 weeks Dosed 3x at 6 week intervals 28 week study	2 injections within 12 weeks: (26), (33), (41), (51), (64)	2.2, 2.75, 3.4, 4.3, 5.3	(79), (99), (123), (153), (192),	0.2, 0.25, 0.31, 0.39, 0.48
442/017	Rabbit IM	2.5, 3.5, 5, 10, 20, 40 LDU/kg Dosing: 4 weeks Dosed 3 x at 2 week intervals 4 week study	3 injections within 12 weeks: (7.5), (10.5), (15), (30), (60), (120)	0.63, 0.88, 1.25, 2.5, 5, 10	(82.5), (115.5), (165), (330), (660), (1320)	0.21, 0.29, 0.42, 0.83, 1.67, 3.33
442/016	Monkey IM	4, 8, 16 LDU/kg Dosing: 12 weeks Dosed 4 x at 4 week intervals 13 week study	3 injections in within 12 weeks: (12), (24), (48)	1, 2, 4	(144), (288), (576)	0.36, 0.73, 1.5
AA41667		4, 8, 12 LDU/kg Dosing: 9 months Dosed 10 x at 4 week intervals 9month study(I)	3 injections in within 12 weeks: (12), (24), (36)	1, 2, 3	(144), (288), (432)	0.36, 0.73, 1.1

Study no.	Species (Route)	NT 201 Dose (U/kg) ^a (Frequency)	12 Weeks Total dose (LDU/kg)	Dose multiples (based on total dose (LDU/kg) in 12 weeks)	12 Weeks Total dose (LDU/m ²) ^b	Dose multiples (based on total dose (LDU/m ²) in 12 weeks)
AA73434		16 LDU/kg Dosing: 12 weeks to 9 months Dosed 4 x at 4, 8 or 12 week intervals 9 month study (II)	4 week interval: 3 injections within 12 weeks (48) 8 week interval: 2 injections within 12 weeks (32) 12 week intervals: 1 injection within 12 weeks (16)	4, 2.7, 1.3	4 week interval: 3 injections within 12 weeks (576) 8 week interval: 2 injections within 12 weeks (384) 12 week intervals: 1 injection within 12 weeks (192)	1.5, 0.97, 0.48
Juvenile toxicity						
AA42070	Rat IM	5, 10, 30 LDU/kg Dosing: 8 weeks Dosed 5 times at 2 week intervals 8-14 week study	5 injections within 12 weeks (25), (50), (150)	2.1, 4.2, 12.5	(150), (300), (900)	0.38, 0.76 2.3
PK in humans	Human (IM)	i) [^] (300U); 6 LDU/kg every 6 weeks = 600 LDU in 12 Weeks 12 LDU/kg in 12 weeks	12 LDU/kg in 12 weeks	NA	396 (U/m ²)	NA

(a): Based on mean body weights recorded at the start of each study for the nonclinical species and 50 kg for humans; (b): Based on respective conversion factors of: mouse: 3, rat: 6, rabbit: 11, monkey 12 and 33 for humans; (^): Maximum dose in humans: for the cervical dystonia indication, cumulative dose not to exceed 300 LDU (6 LDU/kg; for a 50 kg patient) over a 6 week period (data are normalised over an arbitrary 12 week exposure period); NOAELs for systemic toxicity are highlighted in bold; NOAELs for local toxicity were not established; NA = not applicable;

Major toxicities

All the toxicology findings observed for NT 201 were consistent with those of Botulinum toxin type A (BoNT/A) agents as a class. Findings with NT 201 were mainly restricted to the injected (treated) muscle with findings of reduced muscle weights (approximately 40-60% for the treated gastrocnemius and/or biceps brachialis muscles) and muscle atrophy, with some histological evidence of degeneration leading to reduced mobility and, at high doses, reduced body weight gain. Histological evidence of NT 201 treatment for motor end plate destruction was also observed with immuno-histochemical staining for surrogate

markers of denervation (nestin and N-CAM). Histological evidence of partial recovery was also observed in the monkey studies. In addition, in some studies in monkeys, the adjacent and contralateral (untreated) muscles also showed evidence of histological changes; these findings were attributed either to diffusion or distant spread from the injection site or limb disuse. A direct effect of NT 201 following distant spread or diffusion from the injection site resulting in systemic toxicity cannot be fully discounted. There were no clinically relevant adverse local tolerance findings.

Exposure margins at the NOAELs in the pivotal animal toxicology for systemic toxicity corresponded to about 1 to 2 fold (monkey 13 week and 9 month studies) the anticipated clinical exposure. NOAELs for local toxicity were not established. The findings in repeat-dose toxicity studies were predominantly related to the expected pharmacological effects of NT 201 and were generally dose-related. Furthermore, the overall toxicity profile of NT 201 was similar to that of the BoNT/A comparators (Dysport and/or Botox) which were included in some of the studies. There were no severe systemic effects, no unexpected or new adverse effects or other specific organ toxicities. The findings in the repeat dose toxicity studies are consistent with those observed in the single dose studies.

NT 201 induced the expected dose related effects of local muscle paralysis and atrophy of the injected muscle at all doses. At high doses, systemic toxicity was manifested mainly as reduced body weight gain (that is, systemic exposure following diffusion from injection site; see below) that generally correlated with decreased food intake. NOAELs shown below refer to the NOAEL for systemic toxicity.

Reduced body weight gain

Reduced body weight gain with BoNT/A was seen in all species and was usually associated with reduced food consumption. Consequently, the NOAEL was not established in the 28 week mouse study (< 0.262 LDU/animal/injection (< 13 LDU/kg; Exposure Ratio (ER), 2.2-fold the maximum clinical dose; see Table 2 above for details)), with the adverse effect of NT 201 on body weight being comparable to that of Botox. Severe reductions in body weight and slightly reduced food consumption was also observed in the 4 week IM study in rabbits (NOAEL not established; < 2.5 LDU/kg; ER, 0.63).

Significant body weight loss was also observed in a 13 week monkey study at 16 LDU/kg NT 201 (20 % of initial body weight in females, about 10 % in males; findings were similar for Botox). There were no drug-related effects on food consumption. The NOAEL of 8 LDU/kg corresponded to an exposure ratio of 2. In a 9 month monkey study, in animals dosed 10 times at 4 week intervals, body weight gain was significantly reduced at 8 LDU/kg (ER of 2) in both sexes, as well as in females at the low dose of 4 LDU/kg (exposure ratio of 1; NOAEL not established, < 4 LDU/kg) compared to controls. There were no drug-related findings on food consumption. In a second 9 month monkey study, slight drug related body weight loss was also seen in animals of both sexes which were dosed four times at 16 LDU/kg every 4 weeks (exposure ratio of 4), with no treatment related effects on food consumption (the NOAEL was not established, < 16 LDU/kg).

Skeletal Muscle

Expected findings of atrophy of the injected muscle were observed in the two pivotal 9 month repeat dose studies in monkeys. The doses administered corresponded to exposure ratios of 1 to 4-fold the maximum clinical dose; see Table above for details. The finding of atrophy was not dose-related, as reflected in the weights of the injected muscles taken at necropsy (approximately 40% to 70% lower than that of controls). Histological findings of the treated muscles included secondary changes such as slight fibrosis and adiposis.

Absolute and relative weights of contralateral (untreated) muscle also decreased dose-dependently in the 13 week monkey study at 8 (ER, 2) and 16 LDU/kg (ER, 4) and was considered to be either secondary to the weight loss and emaciated condition of animals

or due to changes in their mobility after the induced weakness on the treated side. However, it could also reflect distant spread of NT 201 and systemic toxicity.

Similar observations were reported in the two 9 month monkey studies. Dose-related reduced weights of the contralateral right (untreated) gastrocnemius muscle at 4 12 LDU/kg (ER, 1 3) was proposed to be a secondary effect of the decreased weight of the left (treated) gastrocnemius muscle (that is, due to disuse atrophy); at 8 and 12 LDU/kg slight losses in the absolute weight paralleled the decrease in body weights (that is, decreases in muscle weights were not seen in relative values (only slightly decreased in females)). Similar histological findings of minimal to slight increases of collagen in the (untreated) right gastrocnemius muscle, as well as minimal multifocal increase of adipose tissue were also observed in the muscle connected to the tibia (the soleus muscle, adjacent to the gastrocnemius muscle). Furthermore, histological correlates of a secondary change in the reduction in myofibre size (atrophy) were also detected in control skeletal muscle specimens (left quadriceps femoris muscle). Similar findings were also observed in rats (Study AA77414; primary pharmacology study), where other adjacent muscles on the same limb as the gastrocnemius muscle injection site (quadriceps femoris and gluteus muscles) also showed comparable histological findings to those in the treated gastrocnemius muscle at all doses (although the reduction in fibre size was less severe and reversed earlier; the quadriceps femoris was more affected than the gluteus

In contrast, 2 published studies on the issue of local/distant spread in mice, rats and rabbits showed only a marginal local spread of NT 201 (that is, the purified 150 kDa botulinum toxin) from the intramuscular injection site in the surrounding tissue and/or into the contralateral muscles.

Following a 6 month drug-free recovery period, atrophy was still seen in the left (treated) gastrocnemius muscle correlating with a decreased muscle weight (approximately 50%). Although some signs of partial recovery were observed, the local direct and secondary changes did not reverse completely within a 6-month recovery period. Some histological findings suggested a degree of recovery: immunohistochemistry (nestin staining) of the treated gastrocnemius muscle showed slight diffuse staining and minimal subsarcolemmal staining in the atrophied areas, whereas scattered myofibres which had regained size showed a focal or circular staining (as seen in controls); this probably indicates some myofibres returned to normal (focal/localized nestin staining indicates re-establishment of the neuromuscular junction (NMJ)), whereas other myofibres remained small; diffuse nestin staining indicated that the NMJ had not re-established). The 6 month recovery period was determined to be too short to assess the full potential for recovery of the NMJs. However, following the recovery period, the right (untreated) gastrocnemius muscle showed a similar organ weight compared to controls and did not show any other histological changes indicating complete recovery.

Heart

In the 9 month monkey study (10 injections at 4 week intervals; Study AA41667), treated groups showed a dose-related reduction in mean heart weight. Males treated at the high dose (12 LDU/kg; ER, 2) and treated females (4-12 LDU/kg; ER, 1-3) presented with lower mean absolute and relative heart weight (statistically significant only for absolute heart weight in females at 12 LDU/kg (p less than or equal to 0.01) and 4 LDU/kg (p less than or equal to 0.05); decreases in terminal body weight may account for some of the change in absolute heart weight). There were no functional cardiovascular alterations and no histopathological correlates associated with these organ weight findings. In the second monkey 9 Month IM study (AA73434), males and females dosed at 16 LDU/kg every 4 weeks (high frequency; ER, 4) showed lower absolute heart weight (no statistically significant findings) but not relative heart weight, suggesting the finding was probably associated with the body weight loss in these animals; furthermore, there were no functional cardiovascular alterations and no histopathological findings in the heart also in

this study. On balance, the finding is not considered to be toxicologically relevant, although the biological significance of this finding is not clarified.

Genotoxicity

No studies were conducted. Genetic toxicology tests are not typically required according to the relevant ICH guideline.⁷ The sponsor proposes that *'based on the chemical structure and mode of action of NT 201, there is no reason to suspect any possible mutagenic potential.'* However this statement was not substantiated (for example, with an independent review of the applicability and practicality of assessing the genotoxicity of Xeomin taking into account its physical and chemical nature).

Carcinogenicity

No carcinogenicity studies were conducted. This is acceptable given the nature of the drug⁷ (that is, Xeomin does not show any particular biological activity, has no known growth factor activity and does not target any critical receptor type or specific immunological mechanism), its general lack of systemic exposure in humans and animals following IM administration and its intermittent frequency of use.

Reproductive toxicity

A standard set of GLP-compliant reproductive toxicity studies were submitted and examined both male and female fertility (in rabbits), embryofeotal toxicity (rats and rabbits) and pre/postnatal development (rats). All studies used the IM route of administration. Based on submitted antigenicity studies in rabbits (see below) it is unlikely that anti botulinum toxin type A (BoNT/A) antibody responses occurred (if at all) in rabbits that may have influenced the study results. Adequate animal numbers and dose levels were used during appropriate gestational periods.

Relative exposure

Relative to the maximum recommended dose in humans of 400 LDU (8 LDU/kg for a 50 kg patient given every 12 weeks for the post-stroke spasticity of the upper limb indication), exposure ratios ranged from below one to 15 (that is, rabbit fertility study ER: 0.46-2.2; rat embryofeotal toxicity ER: 1.13-12.25; rabbit embryofeotal toxicity ER: 0.46-1.88; and rat pre/postnatal development ER: 15; see Table below). Since there are no toxicokinetic data available, relative exposures are based on a dose per bodyweight basis (that is, LDU/kg). It is also unlikely that there was continuous systemic exposure of pregnant animals during organogenesis in studies to assess the potential teratogenic effects of NT 201.

⁷ ICH S6: Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals; CPMP/ICH/302/95).

Table 3. NT 201 exposure calculations (Total Dose: (LDU/kg) or (U/m²)) in reproductive toxicity studies

Study no.	Species (Route)	NT 201 Dose (U/kg) ^a (Frequency)	12 Weeks Total dose (LDU/kg)	Dose multiples (based on total dose (LDU/kg) in 12 weeks)	12 Weeks Total dose (U/m ²) ^b	Dose multiples (based on total dose (U/m ²) in 12 weeks)
AA42649 EFD		Daily 7 LDU/kg 14 injections Weekly: 3, 10, 30 3 injections Twice/week: 2, 6, 18 5 injections	Daily: (98) Weekly: (9), (30), (90) Twice/week (10), (30), (90)	Daily: 12.25 Weekly: 1.13, 3.75, 11.25 Twice/week: 1.25, 3.75, 11.25	Daily: (588) Weekly: (54), (180), (540) Twice/week (60), (180), (540)	Daily: 2.23 Weekly: 0.20, 0.68, 2.0 Twice/week: 0.23, 0.68, 2.0
AA81049 PND	Rat	Daily 3 LDU/kg 38 injections Weekly: 2, 6, 20 6 injections	Daily: (114) Weekly: (12), (36), (120)	Daily: 14.25 Weekly: 1.5, 4.5, 15	Daily: (684) Weekly: (72), (216), (720)	Daily: 2.6 Weekly: 0.27, 0.82, 2.73
442/019 Fertility	Rabbit	Males: 1.25, 2.5, 3.5 LDU/kg Dosing: 8 weeks 5 injections at 2 week intervals	(6.25), (12.5), (17.5)	0.78, 1.56, 2.2	(68.75), (137.5), (192.5)	0.26, 0.52, 0.73
		Females: 1.25, 2.5, 3.5 LDU/kg Dosing: 4 weeks 3 injections at 2 week interval	(3.75), (7.5), (10.5)	0.46, 0.94, 1.31	(41.25), (82.5), (115.5)	0.16, 0.31, 0.44
442/018 EFD		1.25, 2.5, 5 LDU/kg 3 injections on GD 6, 18, 28	(3.75), (7.5), (15)	0.46, 0.94, 1.88	(41.25), (82.5), (165)	0.16, 0.31, 0.63

Study no.	Species (Route)	NT 201 Dose (U/kg) ^a (Frequency)	12 Weeks Total dose (LDU/kg)	Dose multiples (based on total dose (LDU/kg) in 12 weeks)	12 Weeks Total dose (U/m ²) ^b	Dose multiples (based on total dose (U/m ²) in 12 weeks)
PK in humans	Human (IM)	8 LDU/kg (400U) ^Every 12 weeks	8 LDU/kg	NA	264 (U/m ²)	

(a): Based on mean body weights recorded at the start of each study for the nonclinical species and 50 kg for humans; (b): Based on respective conversion factors of: rat: 6, rabbit: 11 and 33 for humans; (^): Maximum dose in humans: for the Post-stroke spasticity of the upper limb indication, cumulative dose not to exceed 400 LDU (8 LDU/kg for a 50 kg patient) over a 12 week period; NA = not applicable; NOAELs are highlighted in bold

No studies were conducted to assess either placental transfer of NT 201 or excretion in milk. The justification provided by the sponsor is that there would be low systemic exposure (even assuming full systemic exposure to the clinical dose in the case of inadvertent intravenous administration), and limited placental transfer of BoNT/A due to its large molecular size. In addition, if the complete clinical dose of 400 LDU/injection was transferred to milk, the maximal transfer from the lactating mother would be 0.004 LDU/injection (0.028 pg of neurotoxin) and this is likely to pose a negligible risk of adverse effects to the offspring.

Although F₀ animals displayed toxicity and adverse effects due to the known pharmacological activity of NT201 (slight limb paralysis and body weight loss), male and female fertility were generally unaffected in rabbits following IM administration of NT 201 administered every 2 weeks (starting 2 weeks prior to mating) at doses of less than or equal to 3.5 LDU/kg (ER, males: less than or equal to 2.2, females: less than or equal to 1.31). Although mating was considered unaffected by the sponsor, there was a slight increase in the number of males that failed to mate (control: 1, 1.25 LDU/kg: 2.5 LDU/kg: 2 and 3.5 LDU/kg: 2); in addition, in an embryofetal development study in rabbits, there was an increased incidence of abortions in rabbits at the high dose of 5 LDU/kg which was also maternotoxic (ER, 1.88; 5 of 22 dams aborted on GD23-29; no observable effect level (NOEL) was 2.5 LDU/kg (ER, 0.94)). The current Product Information for Dysport states that there is reduced mating secondary to muscle paralysis at IM doses of 33 LDU/kg per week in male rats and 80 LDU/kg per week in females. The Botox Product Information document states that IM doses of 4 LDU/kg (males) and 8 LDU/kg (females) did not affect rat fertility, but there was reduced fertility at higher doses (associated with signs of toxicity). As for Dysport, the reduced fertility observed for Botox appears to be an indirect effect (secondary to restricted injection limb use and/or body weight loss). All the findings for NT 201 are consistent with those reported for other BoNT/A agents.

In embryofetal development studies in rats and rabbits, maternotoxicity was displayed with animals showing the expected adverse effects including lame hind limbs (limb paralysis) and body weight loss due to the pharmacological effect of NT201 administered IM during the period of organogenesis. Foetal rat weights were slightly reduced at a maternotoxic 'total dose level' of 90-98 LDU/kg⁸ (that is, these doses were associated with a small increase in the incidence of incomplete or lack of ossification (for example, in metacarpal digits, sternbrae and vertebrae) compared to controls. There were similar findings in rabbits following 3 injections at 1.25, 2.5 and LDU/kg (ER, 0.46, 0.94 and 1.88;

⁸ Either i) 14 injections at 7 LDU/kg (7%; p<0.05; ER, 12.25) ii) 3 injections at 30 LDU/kg (ER, 11.25) or iii) 5 injections at 18 LDU/kg groups (ER, 11.25)).

mid- and high doses were maternotoxic). However, the differences were small and comparable with historical control data, showed no dose response, and are not considered to be of toxicological significance. The NOEL for embryotoxicity in rats is a total dose level of approximately 90-98 LDU/kg.⁸ In rabbits, the NOEL is 5 LDU/kg (ER, 1.88). No teratogenicity was observed in rats (ER less than or equal to 12.25) or rabbits (ER less than or equal to 1.88). The reproductive toxicity findings are consistent with those seen with Botox and Dysport.

One question that remains unanswered is the extent to which anti- BoNT/A antibody responses occurred (if at all) in rodents, and may have influenced the study results.

In a pre/postnatal study in rats, mean pup birth weights following treatment at the high dose of 20 LDU/kg (ER, 15) were significantly reduced (7.2 g compared with controls, 7.7 g) for males only. However, the pup birth weight for both sexes combined was unaffected (7.1 g compared with controls, 7.5 g). The NOAEL for pup development was a total of 114 LDU/kg⁹ (ER, 14.25) and a total of 120 LDU/kg¹⁰ (ER, 15) (that is, no overall adverse findings on pre- or post-natal development or reproductive performance despite maternotoxicity of muscle atrophy, paresis and body weight loss). There was a finding unique to this study of localised distension of the abdomen adjacent to injected hind limb, observed after the second injection in some animals at 20 LDU/kg (ER, 15) from Gestational Day (GD) 15 and at 3 LDU/kg (ER, 14.25) from GD 17. During the lactation period, the same finding was seen in majority of animals in both groups as well as some animals dosed at 6 LDU/kg (10/24; ER, 4.5) and probably resulted from diffusion of NT 201 from the injection site.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.¹¹ This is appropriate. The pregnancy categorisation is consistent with other BoNT/A products as a class.

Local tolerance

NT201 (100 LDU/mL in 0.1 mL) was instilled directly into the eye (conjunctival sac) of rabbits to investigate its potential for eye irritation. The cornea, iris and conjunctiva were unaffected following ophthalmoscopic examination with a slit lamp, or following fluorescein-6 administration (cornea). NT 201 was assessed as non-irritating in the rabbit eye.

Antigenicity

Repeat-dose immunogenicity studies were conducted in rabbits using the intradermal route of administration of NT 201. In a 10 week study, the formation of neutralising antibodies against the neurotoxin was assessed following 5 intradermal (intracutaneous) injections at short intervals of 2 weeks at 8.34 LDU/kg (25 LDU per animal) of either NT 201 or Botox.

In Week 12, botulinum toxin type A (BoNT/A) neutralising antibodies were detected in 4 out of 8 surviving rabbits treated with Botox, but in 0 out of 10 surviving rabbits injected with NT 201.

⁹ Thirty eighty daily injections at 3 LDU/kg.

¹⁰ Six weekly injections at 20 LDU/kg.

¹¹ Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

In a second rabbit study, NT 201 or Botox was administered over 33 weeks at 5.34 LDU/kg (16 LDU per animal) for 8 doses, then at 25 LDU (8.34 LDU/kg) for the ninth (final) booster injection; Dysport was administered at 13.34 LDU/kg (40 LDU per animal) for 5 injections and with a decreased dose level of 20 LDU (6.67 LDU/kg) for a sixth (final dose).

At Week 15, serum from 19 out of 20 Dysport-treated animals were positive in an ELISA assay to detect the presence of antibodies; 15 out of 19 of these sera samples subsequently showed neutralising activity in a functional assay (neutralisation of the paralytic activity of the neurotoxin in a mouse hemidiaphragm bioassay).

However, at Week 15, none of the sera from the Botox or NT 201 treated animals was positive for the presence of neutralising antibodies in the mouse hemidiaphragm bioassay; consequently the study was extended to 36 weeks (total of 9 doses). Only 1 out of 20 NT 201-treated animals showed a positive response in the Enzyme linked immunosorbent assay (ELISA) assay and 0 out of 20 (none) had detectable neutralising antibodies. In contrast, 7 out of 20 animals treated with Botox showed a positive reaction in the ELISA and 4 out of 7 of these were positive for the presence of neutralising antibodies in the mouse bioassay.

With regard to immunogenicity assessment in all three repeat dose toxicity studies in monkeys, blood samples were collected for possible immunological assessment. However, no evaluation of actual immunogenicity assessment was carried out and no antibody data were provided. Although NT 201 is purified to remove clostridial complexing proteins, antibodies can still be formed against the BoNT/A neurotoxin itself. Overall, there was limited assessment of the immunogenic potential of NT 201 in the nonclinical dossier (that is, only carried out in 2 rabbit studies). Although these 2 studies showed NT 201 did not result in neutralising antibodies after repeated administration, it is well known that the detection of antibody formation is highly dependent on the sensitivity and specificity of an assay and the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology and sample handling (that is, it appears the assay and corresponding findings might be variable). Therefore, the submitted nonclinical data may be insufficient in scope to allow an overall proper assessment as to the potential immunogenicity of NT 201 with repeated dosing from a nonclinical perspective.

Juvenile Toxicity

In Study AA42070, juvenile rats were administered 5 IM injections of NT 201 (5, 10, 30 LDU/kg (ER, 2.1, 4.2, 12.5, respectively) at 2 week intervals over 8 weeks. Animals were sacrificed 1, 5 or 8 weeks after the last dose. There were no toxicokinetic data in animals to facilitate the assessment of potential risk associated with NT 201. Juvenile animals were given NT 201 by IM injection into the gluteus muscles (alternately into the left or right gluteus muscle) from the age of weaning up to 11 weeks of age. Bone densitometry determinations were also performed; reversibility of the effects were assessed after a recovery period of 7 weeks.

There were findings of the expected atrophy of injected muscles in all groups. Treatment related adverse findings comprised decreased body weight gain (reductions in body weight of about 10-30%) and/or growth retardation in all dose groups, with no effects on sexual maturation and post-weaning development. There were also minimal (significant) findings of slightly reduced tibial length (1 to 3 %) in all dosed males and the majority of females, persisting to the end of the recovery period (1 to 4%); tibial length is a marker of skeletal growth and the finding is consistent with decreases in body weights in the treated animals. Reduced mating performance was observed at 30 LDU/kg ((ER, 12.5); that is, copulation index of 56% compared with controls, 100%) as well as minor findings on other reproductive parameters (litter data) at all doses. These findings were probably

associated with limb weakness and lower body weights, but a direct effect of NT 201 cannot be excluded.

In bone densitometry studies conducted on excised femurs (distal and midshaft) and lumbar vertebrae, there were treatment related findings of both lower bone content (mg/mm), area (mm²) and density (mg/cm³) of the femurs and lumbar vertebrae in all treated groups (dose related and considered to be associated with

- lower body weights of NT 201 treated animals as well as
- a consequence of the physical disability arising from the pharmacologically induced paresis of treated muscles).

However, a direct effect of NT 201 on bone density cannot be excluded. Partial reversal was observed following the recovery period.

Germinal atrophy in the testes and hypospermia in the epididymides was seen at 30 LDU/kg (that is, necropsy findings of small appearance of testes and epididymides correlated with findings at the histopathological assessment of bilateral or unilateral germinal epithelial degeneration and unilateral or bilateral aspermia, respectively). The affected males were not those that failed to mate. Following the recovery period, adverse treatment related findings were seen either at a lower incidence and/or severity, indicating partial reversal. Overall, a direct effect of NT 201 on the testes and epididymides cannot be excluded in view of the macroscopic (small appearance) and microscopic correlates (germinal epithelial degeneration in testes and hypospermia in epididymides) seen at 30 LDU/kg. Given the importance of cholinergic transmission in male reproductive tissues, a direct drug-related effect should not be ruled out.

Overall, the NOAEL for systemic toxicity and post-weaning development was not established due to dose related reductions in body weight at all doses and muscle atrophy (and the secondary consequences on growth which was likely due to the physical disability arising from the pharmacologically-induced paresis of the treated left and right gluteus muscles), respectively. The NOAEL was < 5 LDU/kg (that is, < 25 LDU/kg in 8 weeks).

Haemotoxicity

No haemolysis was seen with NT 101 following incubation of erythrocytes with 100 to 400 LDU/mL.

Paediatric use

The Product Information notes that Xeomin has not been studied in the paediatric population and is therefore not recommended in the paediatric age group. A juvenile rat toxicity study was submitted. Significant findings included dose related reductions in body weight and muscle atrophy and associated secondary consequences on growth, which was likely due to the physical disability arising from injection of the left and right gluteus muscles. Germinal atrophy in the testes and hypospermia in the epididymides was also seen at 30 LDU/kg.

Nonclinical discussion

Xeomin (NT 201) is a Botulinum toxin type A (BoNT/A) muscle paralytic agent belonging to a well-established class of drugs, which has been purified to remove the clostridial complexing proteins that are present in the previously approved products Botox and Dysport. The in vivo primary pharmacology data were consistent with NT 201 producing a long lasting blockade of acetylcholine release at cholinergic nerve terminals and/or the

neuromuscular junction. The muscle paralytic effects of NT 201 appear to be comparable to those of Botox, and a full functional recovery was observed.

Overall, in single and/or repeat dose toxicity studies, the toxicity profile of NT 201 was similar to that of Dysport and Botox. Adverse toxicological findings were consistent with the known class effects of BoNT/A, and were mainly restricted to the injected muscle. There were no clinically relevant adverse local tolerance findings at less than or equal to 40 LDU/kg. Although the NOAEL for systemic toxicity corresponded to exposure levels only 1 to 2-fold higher than the maximum clinical exposure, there was no evidence that it differed in this respect from Botox and Dysport, which have been registered for therapeutic use in Australia for many years. In addition, adequate overseas clinical experience already available with Xeomin possibly mitigates the low exposure margins regarding potential systemic toxicity. The draft Product Information document highlights potential toxicities arising from 'Local /Distant Spread' and the issue is also addressed in the Risk Management Plan as a safety concern.

Although Xeomin is free of complexing proteins, antibodies can still be formed against the neurotoxin itself. Neutralising antibodies were not detected in 2 antigenicity studies in rabbits. The clinical relevance of these data is uncertain, and the potential for neutralising antibody formation needs to be addressed by the clinical evaluator to determine the potential for antibody formation in humans. Presently, this is addressed in the Product Information and Risk Management Plan.

The nonclinical dossier was sufficient in scope and the studies support the proposed indication and the relevant statements in the proposed Product Information (PI).

Non clinical summary and conclusions

- The active substance in NT 201 (Xeomin) is NT 101, which is fermentation derived Botulinum toxin type A (BoNT/A) that has been purified to remove the clostridial complexing proteins (haemagglutinin and non-haemagglutinins) present in previously approved BoNT/A products (Botox, Dysport) that do not contribute to the therapeutic paralytic effect.
- The non-clinical submission consisted of well-designed and documented studies in rats, mice, rabbits and monkeys, conducted in compliance with GLP requirements when required, and generally conformed to relevant ICH guidelines. The submission relied in part on published studies.
- Nonclinical studies were conducted to establish the safety and toxicity profile of Xeomin and to assess possible differences in potency, safety, local or systemic spread and antigenicity (ability to generate neutralising antibodies) after IM injections compared to Botox and Dysport.
- Three primary pharmacological studies confirmed that NT 201 acts on the neuromuscular junction and muscles producing the desired effect of reducing muscle tension and paralysis. The time course of onset, maximum paralytic efficacy and recovery time were comparable to Botox and Dysport.
- Safety pharmacology studies covered the CNS, cardiovascular (ECG parameters) and gastrointestinal systems. ECG abnormalities were not observed in NT 201 treated animals. There are no specific concerns raised from the safety pharmacology studies.
- Standard kinetic studies cannot be performed with NT 201 since it is given in small quantities (picograms per injection) and it binds so rapidly and irreversibly to cholinergic nerve terminals. Two published kinetic studies using mice, rats and rabbits showed the purified toxin (150 kDa) and the 900 kDa toxin complex have similar tissue distributions, and diffusion from injection sites is negligible.

- Local injection site toxicity or the potential toxicity that might result from systemic exposure in humans was determined in single dose toxicity studies (IM, IV, intraperitoneal (IP) and oral (PO) dosing routes) in mice and rats and pivotal IM repeat dose toxicity studies in monkeys. Toxicity studies included the clinically relevant route (IM). In all submitted studies, the toxicity profile of NT 201 was similar and/or comparable to that of Dysport and Botox.
- In acute toxicity studies, mortality probably occurred as a result of the pharmacological action of NT 201 on respiratory muscles, accompanied by additional findings of local (treated) muscle paralysis (resulting in reduced mobility, muscle tone and ataxia) and/or low grade blockade of autonomic neurotransmission (piloerection, ptosis, lacrimation, mydriasis). No unexpected findings or other specific organ toxicity according to the drug class was observed. Systemic toxicity (manifested as paralysis of distant respiratory muscles following IM administration) could be a theoretical clinical risk based on low exposure margins of 0.6-fold at the NOAEL, compared to the maximum clinical dose. However, NT 201 displayed similar potency to Botox in mouse lethality assays (LD50 values) following dosing by the IM and IV routes. Additionally, NT 201 showed a similar degree/profile of toxicity to Botox, without any qualitative differences, and there were no novel toxicities.
- Pivotal repeat-dose toxicity (IM) studies were conducted with NT 201 in rabbits and monkeys. Toxicological findings were mainly restricted to the injected (treated) muscle (that is,, reduced muscle weight, atrophy/degeneration and associated histopathological changes, reduced mobility and decreased overall body weight gain). In some studies, the adjacent and contralateral (untreated) muscles also showed reduced muscle weight and evidence of histological changes which were attributed to diffusion/distant spread from the injection site and limb disuse, respectively. Distant spread/diffusion resulting in systemic toxicity cannot be fully discounted. All of these findings are well known class effects of BoNT/A agents.
- Since NT 201 induced the expected atrophy of the injected muscle at all doses, NOAELs for local toxicity were not established and consequently, definitive NOAELs were not established in any of the submitted repeat dose toxicity studies. For systemic toxicity, at the NOAELs reported in the monkey 13 week and 9 month IM studies, estimated exposure (based on dose normalised over time) was only 1 to 2-fold higher than the maximum estimated clinical exposure. However, overall, the findings suggest that there were no notable differences in the toxicological profiles of Xeomin, Botox and Dysport in repeat dose studies in mice or monkeys.
- In a juvenile rat toxicity study, dose related reductions in body weight and muscle atrophy and associated secondary consequences on growth were likely due to the physical disability arising from muscle paralysis. Germinal atrophy in the testes and hypospermia in the epididymides were also observed.
- Fertility was generally unaffected in male and female rabbits. However, in an embryofeotal development study, there were findings of increased incidence of abortions in rabbits. Adverse effects of delays in ossification in rats and rabbits as well as decreased foetal weight in rats were seen after maternal dosing. Placental transfer of NT 201 and excretion in milk was not investigated. There was no indication that NT 201 was teratogenic. In addition, it had no effect on pre- and postnatal development. All findings were consistent with those reported for other BoNT/A agents as a class.
- NT 201 was non-irritating in the rabbit eye.
- In two 10-36 week antigenicity studies in rabbits (intradermal route; up to 8.34 LDU/kg), NT 201 administration did not result in neutralising antibodies after repeated administration. However, neutralising antibodies were observed following

treatment with Botox or Dysport. No evaluation of immunogenicity was carried out in pivotal repeat dose studies in monkeys.

There are no nonclinical objections to the registration of NT 201 (Xeomin) for the proposed indications.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

NT 201 (Xeomin) is a member of the class of drugs referred to as botulinum toxins, of which the most well-known is Botox. These toxins are produced in nature by the bacterium, *Clostridium botulinum*, and contribute to the clinical paralytic syndrome of botulism that sometimes results from clostridial infection. The agents have been adopted for topical therapeutic use in situations where local muscle weakness is desirable, such as conditions characterised by spasticity, dystonia or other muscle hyperactivity.

NT 201 differs from Botox and other members of this class in that it lacks the complexing proteins that normally accompany the toxin.

Clinical rationale

For a range of neuromuscular conditions, overactivity of muscles is a major contributor to disability, and botulinum toxin preparations have been useful in ameliorating symptoms. Such conditions include spasticity and dystonia, for which there are only limited therapeutic options.

Anti-spasticity drugs include baclofen and some anticonvulsants such as valproate or benzodiazepines, but these agents are usually administered systemically and often produce unacceptable drowsiness. Some dystonias respond to levodopa or dopamine agonists, but the response is often unsatisfactory.

Cervical dystonia, in which patients experience unwanted, involuntary head turning, is an uncomfortable condition that may impair motor function and produce social stigma and isolation.

Blepharospasm, which is usually considered a dystonia of the muscles closing the eye, is also disfiguring and socially isolating, but can in addition produce functional blindness if patients are unable to open their eyes.

Botulinum toxin treatment provides a useful alternative to systemic treatment for these conditions, because it is injected into the target muscles and has few or no systemic side effects. It has therefore become a widely accepted treatment, usually administered in specialised clinics by neurologists or rehabilitation physicians.

Botulinum toxin has also been used to treat facial wrinkles. There is no strong clinical rationale for such treatment, but there has been extensive experience with this approach and the overall safety profile of existing botulinum toxins when used for cosmetic purposes is acceptable.

The new agent NT 201 does not offer any major changes in efficacy or safety over existing botulinum agents, but it is a simpler preparation than Botox because it lacks the complexing proteins that normally accompany the bacterial toxin. These proteins do not

contribute to the functional effects of botulinum toxin, and dissociate from the toxin soon after injection¹², but the complexing proteins are likely to contribute to the overall antigenic stimulus associated with the injection of foreign protein. NT 201 would therefore be expected to be less immunogenic than complexed forms of the toxin.

The sponsor has submitted some evidence, based on animal studies, supporting this idea; these studies show that neutralising antibodies are produced less commonly after NT 201 administration than after other botulinum toxin preparations.

Although NT 201 is proposed as a new chemical entity, it is equivalent to the active agent of existing products, the clinical rationale for which is already well-established.

Contents of the clinical dossier

The application to register NT 201 is primarily based on eight pivotal Phase III studies, five of which were double-blind and placebo-controlled (Study 0724 (GFL), Study 0741 (GFL), Study 0408/1 (CD), Study 0433/1 (BLEPH), and Study 0410/i (SP)).

In addition, the sponsor submitted two non-inferiority double-blind, active-controlled studies in comparison with Botox (Study 0013/1 (CD), Study 0003/1 (BLEPH)) and one controlled observer-blind, parallel-group Phase III study with two different dilutions of NT 201 (Study 0607/1 (SP)).

The contents of the submission are summarised below:

- Three clinical pharmacology studies, all of which provided pharmacodynamic (PD) data.
- No pharmacokinetic (PK) studies, which is appropriate given the toxic nature of NT 201 and its topical application.
- Eight pivotal Phase III trials (0724, and 0741 (GFL), 0408 and 0013 (CD), 0433 and 0003 (BLEPH), 0410 and 0607 (SP)).¹³
- Several supportive efficacy studies, including Study 0527 (GFL), a randomised, double-blind, placebo-controlled, Phase II dose finding study, Study 520 (GFL), Study GL 3001 (GFL), which was uncontrolled, Study GL 3002 (GFL) in comparison with Vistabel, Study 9801 (CD) in comparison with Botox, Study 0013/1 (CD) in comparison with Botox, Study 0003/1 (BLEPH), in comparison with Botox and Study 0607/1 (SP), which assessed different dilutions of NT 201.
- Repeated-dose studies, including pooled long-term, repeated-dose safety data from studies with multiple administrations of NT 201: Study 0609 and its lead-in Studies 0520, 0527, 0724, and 0741 for the glabellar frown lines (GFL) indication; Study 0408/1 (Main Period) and 0408/2 (Extension Period), and Study 0605/1 (Main and open label extension (OLEX) Period) for the cervical dystonia (CD) indication; Study 0433/1 (Main Period) and 0433/2 (OLEX Period) for the blepharospasm (BLEPH) indication; and Study 0410/1 (Main Period) and 0410/2 (OLEX Period) for the spasticity (SP) indication.

¹²Sponsor clarification: *'The Botulinum toxin complex (900 kDa) dissociates largely upon reconstitution and dilution in the vial and completely upon IM injection into the neutral pH tissue environment.'* From Studies on the dissociation of botulinum neurotoxin type A complexes. Eisele KH, Fink K, Vey M, Taylor HV. *Toxicol.* 2011 Mar 15;57(4):555-65.

¹³In the study summaries, the sponsor abbreviated the study names to improve readability, and this evaluation report follows the same conventions. The prefixes 'MRZ 60201-' and 'BTC-60201' have been removed from the titles of individual studies, and the indication being studied has been added in parentheses (that is, glabellar frown lines (GFL), cervical dystonia (CD), blepharospasm (BLEPH), spasticity (SP), or healthy volunteer (HV)). The suffix "/1" indicates the main period of a study, and "/2" indicates the extension period.

- An Integrated Summary of Efficacy and an Integrated Summary of Safety.
- The sponsors clinical overview, summary of clinical efficacy, summary of clinical safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

For each submitted study, a declaration was provided indicating that the study had conformed to Good Clinical Practice guidelines.

Pharmacokinetics (PK)

Studies providing pharmacokinetic data

No pharmacokinetic (PK) studies, which is appropriate given the toxic nature of NT 201 and its topical application.

Evaluator's conclusions on pharmacokinetics

Conventional PK studies cannot be performed with botulinum toxin in any of its forms, because it is extremely toxic when administered systemically. It is always administered locally, in very small quantities (picograms of toxin per injection), directly at the intended site of action or within a short distance of the intended target; it then spreads over a limited distance by local diffusion. The NT 201 preparation is no different to existing botulinum toxin preparations in this regard.

Even though NT 201 represents a new preparation of botulinum toxin, it is expected to have similar diffusion characteristics to standard botulinum toxin preparations. Botox, for instance, consists of the same neurotoxin as NT 201, with an identical amino-acid sequence, but is associated with complexing proteins. These proteins dissociate from Botox and other marketed forms of the neurotoxin almost immediately after intramuscular injection¹⁴; from that step onwards, the diffusing properties of the different preparations would be expected to be similar.

Some measure of the diffusing kinetics of NT 201 was provided by the PD study, Study 0709, in which NT 201 was injected into the forehead and the subsequent area of anhidrosis assessed. In this study, the diffusion of NT 201 appeared similar to the competing products Vistabel and Dysport.

Overall, no new PK issues are raised by the proposed introduction of NT 201.

Pharmacodynamics (PD)

Studies providing pharmacodynamic data

The sponsor submitted three PD studies.

¹⁴Sponsor clarification: *'The Botulinum toxin complex (900 kDa) dissociates largely upon reconstitution and dilution in the vial and completely upon IM injection into the neutral pH tissue environment.'* From Studies on the dissociation of botulinum neurotoxin type A complexes. Eisele KH, Fink K, Vey M, Taylor HV. Toxicon. 2011 Mar 15;57(4):555-65.

Two of the Studies (9901 and 0113) investigated the effect of NT 201 on muscle activity in healthy volunteers, as measured by the compound motor action potential (CMAP) in comparison to Botox.

The third Study (0709) assessed the effect of NT 201 on sweating, by measuring the area of anhidrosis following an injection, in comparison to the commercial products Vistabel and Dysport; this is primarily an assessment of the different drugs' diffusion characteristics.

None of the PD studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The submitted PD evidence was limited in scope, and one of the three submitted PD studies appeared unreliable because of a high number of protocol deviations.

On balance, the evidence suggests that NT 201 has a similar potency and similar time course of action compared to other botulinum toxin products, consistent with the notion that other agents including Botox dissociate to produce free toxin that is identical to NT 201.

Dosage selection for the pivotal studies

Given PD evidence suggesting dose equivalence between NT 201 and Botox, the doses used in pivotal studies were either based on treatment guidelines developed for Botox, in the case of treatment-naïve subjects, or consisted of the patients' previous Botox dose.

Efficacy

Studies providing efficacy data

The sponsor designated eight studies as pivotal – two studies for each indication. Many of the studies had an open-label extension, but these extensions are described separately. One of the studies designated as pivotal (0607) did not have a non-NT 201 control group, and should be considered supportive. Discussion of these studies may be found in Attachment 2 (Clinical Evaluation Report (CER) extract).

Evaluator's conclusions on efficacy

Efficacy of NT 201 has been established for all four of the indications sought:

- glabellar frown lines,
- cervical dystonia,
- blepharospasm and
- spasticity.

Pivotal studies in each indication showed highly significant superiority of NT 201 over placebo. Two pivotal Botox-controlled studies were also performed; one in cervical dystonia (0013) and one in blepharospasm (0003), and these showed non-inferiority of NT 201 according to pre-specified equivalence criteria.

All of the pivotal studies achieved their primary aim based on prospectively identified statistical methods, apart from the two pivotal studies of glabellar frown lines, where a zero response rate in the placebo group forced the sponsor to change statistical techniques. Secondary and tertiary endpoints across all four indications were consistent

with the primary endpoints. On balance, the pivotal studies were well-conducted and free of significant methodological flaws, but one of the studies designated as pivotal (0607) merely compared two dilutions of NT 201 in the treatment of spasticity, and lacked a non-NT 201 treatment arm. It therefore does not provide robust evidence of efficacy, though efficacy in this indication was shown in another pivotal study (0410).

A range of supportive studies were also submitted, which were broadly consistent with the pivotal studies.

Repeat dose studies showed no evidence that the efficacy of NT 201 wanes with repeat dosing, but repeat doses were unblinded and uncontrolled, making it impossible to draw firm conclusions.

Safety

Studies providing safety data

All of the studies described in this report contributed safety data, including the 8 pivotal studies, their open-label extensions, and the minor supportive studies. The three pharmacodynamic studies in healthy volunteers also contributed data, but the doses used were low. The safety database also including Study 0617, in which NT 201 was used to treat 'Crow's Feet' (CF) wrinkles.

The sponsor identified two major pools of safety data in the Integrated Summary of Safety: the single-dose placebo-controlled studies, which provide the best evidence of side effects attributable to treatment, and the single-dose, active-controlled studies, which allow comparison of the side effect profile of NT 201 in relation to competing products. The combination of these two pools was also analysed. Repeat-dose studies were also assessed, but this pool of data is less useful because it lacks a comparator.

A total of 2,068 patients were treated with NT 201 in single-dose studies, and 1,313 of these also entered repeated-dose studies.

Safety monitoring was typical of a large clinical program for a new agent, and was acceptable overall. In all studies, subjects and their investigators reported adverse events (AEs) at regular scheduled visits. In addition, any unscheduled clinic or hospital attendances were noted. Narrative summaries were provided for any major events.

For NT 201, which is administered locally, the safety implications depend strongly on the site of injection. In particular, given the known side effect profile of botulinum toxin, which includes unwanted weakness in injected muscles or neighbouring muscles, the sponsor specifically searched the AE database for events suggestive of toxin-induced weakness. Other complications directly related to the interruption of cholinergic transmission include dry eyes and dry mouth, which were also considered AEs of special interest.

Routine laboratory monitoring was performed in all studies. All major studies included an assessment of the immunogenicity of NT 201.

Discussion of these studies may be found in the CER extract.

Patient exposure

Patient exposure to NT 201 in the pooled single-dose studies is summarised below. A total of 2,068 patients were treated. More than half of these (1,067) received NT 201 for GFL, and therefore received a low dose (range 10-30 U). Higher doses were tested in the CD population (n = 431, median dose 120 U) and in the treatment of spasticity (n = 265, median dose 300 U). Medium doses were administered in subjects with blepharospasm

(n = 222, median dose 50 U). The number of subjects with Crow's Feet (CF) was low (n = 83); this population received a dose (24 U) similar to that used in GFL.

Cumulative exposure was more substantial in the repeated-dose studies, summarised below. Over a thousand patients (1,313) were involved in repeated-dose studies, and all of the major sites and indications were assessed.

Safety issues with the potential for major regulatory impact

Liver toxicity

As discussed in the CER, the incidence of hepatic dysfunction was low in the submitted studies. Liver toxicity is not a feature of treatment with other botulinum toxins, and there does not appear to be a significant risk of hepatotoxicity with NT 201.

Haematological toxicity

The haematological data do not suggest that NT 201 has any significant effects on bone marrow function or cell counts.

Serious skin reactions

Serious skin reactions were not reported as TEAEs. According to the sponsor, local allergic reactions have emerged as a safety concern during post-marketing surveillance, but the extent of the problem is unclear from the sponsor's submission. This should be clarified.

Cardiovascular safety

There is no evidence of significant cardiovascular risk with NT 201 treatment. Vital signs and ECG monitoring did not show significant differences between NT 201 and placebo, and cardiovascular AEs occurred at the expected rate in NT 201 recipients.

Unwanted immunological events

Immunological events occurred at a low incidence in NT 201 recipients and placebo recipients, and were generally thought by investigators to be unrelated to treatment. According to the sponsor, however, flulike symptoms and local allergic reactions have emerged as a safety signal during post-marketing surveillance. The nature of this safety signal should be clarified.

Post marketing data

In addition to extensive post-marketing experience with closely related products, such as Botox, there is also some post-marketing data available for NT 201, which was approved in Europe in 2005.

According to the sponsor:

'Since the launch of the product in Germany on 01 July 2005, approximately 127,500 subjects worldwide have been treated with NT 201. Treatment with NT 201 shows good efficacy, and is safe and well-tolerated. For current safety data, please refer to the most recent Periodic Safety Update Report (PSUR). To date, the post-marketing safety analysis has not revealed any new safety signals except for local allergic reactions and flu-like symptoms.'

The nature of these safety signals was not discussed in the sponsor's Integrated Summary of Safety, and the sponsor should be asked to clarify this.

Evaluator's conclusions on safety

Overall, the safety of NT 201 is acceptable. The main risks associated with treatment are those already faced by patients being treated with existing botulinum toxin preparations.

The most significant toxicity issue is the development of excessive weakness in targeted muscles or unwanted weakness in neighbouring muscles. This can be manifested as eyelid ptosis, following injection near the eye, dysphagia or dysarthria, following injection in the neck, or limb weakness following injection in the limbs. Interference with autonomic function may also occur, leading to dry eyes or dry mouth, though the incidence of these problems was low in the submitted studies. These side effects are intrinsically related to the drugs mode of action, and can be minimise by careful dose titration and by restricting use of the drug to experienced operators.

Other safety concerns arise from the fact that NT 201 is a foreign protein, and has some immunogenicity, though this appears less than with other botulinum toxin preparations. The sponsor mentions that flu-like symptoms and local allergic reactions have emerged as safety signals during the post-marketing experience of this drug, and this should clarified. Such symptoms were not prominent during the submitted studies, so it seems unlikely that this will turn out to be a major safety issue.

First round benefit-risk assessment

First round assessment of benefits

The benefits of NT 201 in the proposed usages are:

- Reduction in glabellar frown lines, with a response rate of at least 54% compared to 0% with placebo;
- Amelioration of cervical dystonia that is clearly superior to placebo and equivalent to that achieved with Botox ;
- Reduction in blepharospasm that is clearly superior to placebo and equivalent to Botox;
- Reduction in post-stroke spasticity that is superior to placebo

First round assessment of risks

The risks of NT 201 in the proposed usage appear to be the same as with existing botulinum preparations, and the registration of NT 201 would not be expected to pose any significant new risks.

The main complications of NT 201 are those related to excess weakness in the injected muscles or neighbouring muscles, and dry eyes or dry mouth.

The sponsor reports that post-marketing surveillance has revealed some risk of allergic responses, but the details of this risk have not been well characterised. Unwanted immunological events in the submitted studies were rare.

First round assessment of benefit-risk balance

The benefit-risk balance of NT 201, given the proposed usage, is favourable.

First round recommendation regarding authorisation

The clinical evaluator recommends that NT 201 should be approved for the proposed indications.

Clinical Questions

Safety

The Risk Management Plan (RMP) mentions that post-marketing surveillance has identified. The sponsor should be asked to clarify this.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP, version 5.1, dated 7 October 2010; Australian Specific Annex, dated February 2013 which was reviewed by the TGA.

All figures and tables in this section that have been copied from the original dossier are considered by the evaluator to be an accurate representation of the reviewed data, unless qualified as such in the commentary of the report.

Table 4. Summary of EU risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Local and systemic toxin spread	Systematic and continuous capture and follow-up of all reports of toxin spread ADRs Regular and specific reporting of toxin spread ADRs in PSURs Monitoring of utilization patterns of Xeomin® / Bocouture® as to approved indications and contraindications	Educational material for physicians Educational material for patients Monitoring of off-label use
Dysphagia	Systematic and continuous capture and follow-up of all reports of dysphagia ADRs Regular and specific reporting of dysphagia ADRs in PSURs	Educational material for physicians Educational material for patients Already implemented: Warning in section 4.4 of the SmPC that patients with a history of dysphagia and aspiration should be treated
		with extreme caution.
Antibody formation	Systematic and continuous capture and follow-up of all reports of ADRs possibly based on antibody formation Antibody formation will be assessed in all clinical studies and discussed in RMP	Already implemented: Warning in section 4.4 of the SmPC that too frequent dosing of Botulinum toxin may result in antibody formation which may lead to treatment resistance
Hypersensitivity	Systematic and continuous capture and follow-up of all reports of hypersensitivity ADRs Regular and specific reporting of hypersensitivity ADRs in PSURs	Already implemented: Contraindication in section 4.3 of the SmPC
Patients with pre-existing neuromuscular diseases	Systematic and continuous capture and follow-up of all ADR reports in patients with pre-existing neuromuscular diseases Regular and specific reporting of ADRs in patients with pre-existing neuromuscular diseases in PSURs	Already implemented: Warning in section 4.4 of the SmPC that Xeomin should be used with caution in patients suffering from amyotrophic lateral sclerosis or other diseases which result in peripheral neuromuscular dysfunction

Table 4. Summary of EU risk management plan

The relevant sections of the EU Summary of Product Characteristics (EU SmPC) referenced in the EU-RMP correspond to the following sections in the Australian Product Information (PI):

<u>EU SmPC</u>	<u>Australian PI</u>
Hypersensitivity Section 4.3 (Contraindications)	Contraindications
Toxin spread, dysphagia, antibody formation and patients with pre-existing neuromuscular diseases Section 4.4 (Special Warnings and Precautions for Use)	Precautions

Comments on the safety specification of the RMP

Clinical evaluation report

The sponsor submitted a copy of the latest European RMP, along with an Australian-specific annex.

Distant and local toxin spread had been identified as a safety issue in the original European RMP, and four issues were identified as new since the previous European RMP:

- dysphagia,
- formation of antibodies,
- hypersensitivity, and
- use in patients with pre-existing neuromuscular diseases.

For each of these issues, the primary mechanism for minimising risk was the inclusion of appropriate warnings in the Product Information sheet, and a recommendation that NT 201 be administered by trained operators. To cover the risk of serious allergic reactions, it is recommended that adrenaline be available for the treatment of potential anaphylactic reactions.

According to the RMP, the European Summary of Product Characteristics (SmPC) was also altered to include the following warning: *'In rare cases, localised allergic reactions, such as swelling, oedema, erythema, pruritus or rash, have been reported after treating vertical lines between the eyebrows (glabellar frown lines) and other indications.'*

The SmPC also includes the following statement: *'An anaphylactic reaction may occur rarely after injection of Botulinum neurotoxin type A (See ADVERSE REACTIONS). Adrenaline and other medical aids for treating anaphylaxis should be available.'*

The Australian PI is less specific than this, and contains no direct mention of the need to have adrenaline available: *'Hypersensitivity reactions have been reported with Botulinum neurotoxin products. If serious (for example anaphylactic reaction) and/or immediate hypersensitivity reactions occur, appropriate medical therapy should be instituted.'*

The Australian PI should be altered to match the European SmPC, in line with the concern expressed in the RMP, and should include specific instructions to have adrenaline available at the time of injecting NT 201.

Overall, the Safety Specification in the draft Risk Management Plan was satisfactory, but the issues raised in the RMP should be reflected more clearly in the Australian PI.

Non-clinical evaluation Report

There are no new nonclinical or toxicological signals of concern arising from the sponsor submitted studies. No changes to the nonclinical safety specification of the Risk Management Plan are suggested.

Reconciliation of issues outlined in the RMP report

Table 5 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised and the TGA's evaluation of the sponsor's responses.

Table 5. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Extracts of sponsor's response (for full details refer to the attached s31 response document)	OPR evaluator's comment
It is recommended that EU-RMP, version 5.1, dated 7-Oct-2010; Australian Specific Annex, dated Feb-2013 and any future updates are implemented as a condition of registration.	EU-RMP, version 5.2, dated 06 September 2013; Australian Specific Annex, dated October-2013 submitted with this response and any future updates will be implemented as a condition of registration.	This is considered acceptable.
It is recommended that the sponsor adds use in children as missing information to the table of ongoing safety concerns. Pharmacovigilance and risk minimisation activities should be assigned as appropriate.	Use in children will be added as missing information to the table of ongoing safety concerns. Pharmacovigilance activities will be assigned as appropriate.	This is considered acceptable.

Recommendation in RMP evaluation report	Extracts of sponsor's response (for full details refer to the attached s31 response document)	OPR evaluator's comment
<p>It is recommended that the sponsor adds patients > 60 years, patients with renal, hepatic, or cardiovascular impairment as missing information in the table of ongoing safety concerns. Risk minimisation activities and pharmacovigilance activities should be assigned as appropriate. Regarding risk minimisation activities, it is specifically recommended that the sponsor amends the PI to reflect that no information is available for use of the product in these patient populations.</p>	<p>Regarding patients > 60 years the sponsor has provided a statement: Meanwhile data from 232 patients (> 65 years) have been analysed in the pooled placebo-controlled studies of NT 201. No consistent pattern of increased incidence rates of adverse events was identified for any demographic group. The overall incidence rate of ADRs in elderly (> 65 years) does not differ from the other age groups (<= 50 years, >50-65 years).</p> <p>Regarding patients with renal, hepatic, or cardiovascular impairment the sponsor states that "systemic affects are not expected, and therefore are not considered "important missing information."</p>	<p>The recommendation made by the RMP evaluator relates to the point that it appears that patients 60-65 years have not been systematically studied, but the proposed indication is for patients up to 65 years (this includes patients 60-65 years). The sponsor elaborates in the s31 response that 232 patients > 65 years were meanwhile analysed. The sponsor does not provide the number of patients analysed >50-65 years, and more importantly the number of patients analysed 60-65 years. Consequently, the s31 response does not address the recommendation made by the RMP evaluator. It is recommended that the sponsor adds patients > 60 years as missing information in the table of ongoing safety concerns. Risk minimisation activities and pharmacovigilance activities should be assigned as appropriate.</p> <p>The systemic spread of the product after local administration is an identified risk and is listed in the table of ongoing safety concerns in the RMP. Consequently, systemic affects are considered possible to occur and therefore, risk minimisation and pharmacovigilance should be implemented by the sponsor. It is recommended that the sponsor adds patients with renal, hepatic, or cardiovascular impairment as missing information in the table of ongoing safety concerns. Risk minimisation activities and</p>
AusPAR Xeomin botulinum toxin type A Merz PM-2012-04159-1-1 10 September 2015		<p>pharmacovigilance activities should be assigned as appropriate.</p>

Recommendation in RMP evaluation report	Extracts of sponsor's response (for full details refer to the attached s31 response document)	OPR evaluator's comment
<p>It is brought to the Delegate's attention that the proposed indication for the product is for patients ≥ 65 years although it appears that patients over 60 years were not systematically studied. Moreover, given the proposed indications for the product, it is considered that a high number of patients will be elderly patients.</p>	<p>The proposed indication for the product is for patients below 65 years, not ≥ 65 years as stated under this point.</p>	<p>This recommendation remains unresolved.</p> <p>It is brought to the Delegate's attention that the proposed indication for the product is for patients ≤ 65 years although it appears that patients over 60 years were not systematically studied. Of relevance, given the proposed indications for the product, it is considered that a high number of patients will be elderly patients. (please also refer to point 3)</p>
<p>It is recommended that the sponsor submits the final data of studies (MRZ 60201-0047-0 and MRZ 60201-4059-0) to the TGA for review prior to approval. It is also recommended that the sponsor includes a statement on how these final study results impact on the RMP version provided for assessment.</p>	<p>The final data of studies (MRZ 60201-0047-0 and MRZ 60201-4059-0) will be submitted to the TGA and are attached to this response. The study results do not impact on the RMP version provided for assessment and do not change the risk benefit assessment of the product.</p>	<p>It is noted that the sponsor states: The study results do not impact on the RMP version provided for assessment and do not change the risk benefit assessment of the product.</p> <p>Based on this statement this recommendation is considered to be acceptably addressed.</p>

Recommendation in RMP evaluation report	Extracts of sponsor's response (for full details refer to the attached s31 response document)	OPR evaluator's comment
<p>It is recommended that, the sponsor implements additional pharmacovigilance activities to gather information about off-label use of the product in Australia and associated side effects. Details about the additional activities to be implemented by the sponsor should be provided to the TGA for review prior to approval.</p>	<p>The applicant is aware that by screening the scientific literature - as proposed in the RMP - only a fraction of off-label use will be captured. Additionally individual ADR reports will be monitored for off-label use in due consideration of cases from Australia.</p> <p>Xeomin is a specialty neurology product that trained physicians use for treatment of particular indications, usually in the hospital setting. The applicant is not aware of any commercially available data sources that would allow for a valid and reliable monitoring of drug consumption in the required granularity, that is on indication level.</p> <p>A revised Risk Management Plan, version 5.2, dated 06 September 2013 together with an overview of the changes and an updated Australian Specific Annex (October 2013) is included.</p>	<p>The sponsor proposes the same measures to monitor off-label use as it was proposed in the previous RMP version. The sponsor states: Off-label use will be monitored qualitatively by regular screening of the scientific literature for articles which present experience with the use of Botulinum neurotoxin A in unapproved indications. These articles will be summarised in the PSUR and safety results will be discussed. Additionally all reported ADRs in patients which were treated in an unapproved indication will be monitored with special regard to Australian patients.</p> <p>The added sentence only describes a routine pharmacovigilance activity and consequently, does not acceptably address the recommendation made in the round 1 RMP evaluation report. As described in the round 1 RMP report there is a high potential for off-label use for the product, and it is recommended that the sponsor implements additional pharmacovigilance activities to monitor and report off-label use in Australia. The proposal for this additional pharmacovigilance activity to monitor off-label use should be reviewed by the RMP section prior to approval.</p>

Recommendation in RMP evaluation report	Extracts of sponsor's response (for full details refer to the attached s31 response document)	OPR evaluator's comment
<p>It is recommended that the sponsor provides the educational materials for physicians and patients to be used in Australia for review prior to approval. Moreover, the sponsor should clarify how distribution of these documents will be controlled.</p>	<p>The educational materials for physicians and patients to be used in Australia will be submitted and are included in this response. Further adaptation may be required after final approval of the PI.</p> <p>Merz has established a process for following-up the measures that are defined in the RMP. The distribution of the Educational materials for physicians and patients for NT 201 (tradenames in EU: Xeomin and Bocouture) and tracking of its national implementation in the individual European countries are covered by Merz' SOP 10577. This process was described by the sponsor.</p>	<p>The educational materials have been submitted and appear to be acceptable.</p> <p>However, it is recommended that the sponsor comments on how the effectiveness of the educational materials will be evaluated. It appears important to implement an additional activity to monitor the effectiveness, and to amend the materials, if it is found that they are not effective in their current form to ensure the safe use of the product in the Australian market.</p>
<p>The sponsor should clarify if the Investigators Brochure as a measure to prevent the occurrence of hypersensitivity reactions will also be used in Australia. This brochure should be submitted to the TGA for review prior to approval.</p>	<p>The Investigators Brochure contains the product information for investigators in clinical trials during the development phase of a product. After approval of the product the PI is the relevant document which includes all information for physicians. The information relevant to prevent the occurrence of hypersensitivity reactions is the same in both documents.</p>	<p>This is considered acceptable.</p>

Recommendation in RMP evaluation report	Extracts of sponsor's response (for full details refer to the attached s31 response document)	OPR evaluator's comment
<p>It is recommended that the sponsor amends the PI as follows:</p> <p>A.) It is recommended that the sponsor deletes the following statement from the proposed Australian PI (please refer to section 9.2-potential for medication errors). Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum neurotoxin type A complex (900 kD) are of equal potency when used in a dose conversion ratio of 1:1.</p> <p>B.) It is recommended that the sponsor amends the PI to emphasise that only physicians who are appropriately trained and experienced in the use of botulinum toxin may administer the product. The current wording in the PI is: Xeomin may only be administered by health care professionals. Suggested wording: Xeomin may only be administered by medical practitioners with suitable qualifications and proven experience in the application of Botulinum toxin and in the use of the necessary equipment, for example electromyography (EMG).</p> <p>C.) It is recommended that the sponsor amends the PI to reflect that no information is available for use of the product in patients over 60 years, patients with renal, hepatic, or cardiovascular impairment.</p>	<p>The PI and CMI have been amended to incorporate recommendations only. As recommended in the RMP evaluation report, Section 11, no changes have been made to the PI pending receipt of the Delegate's overview.</p>	<p>The RMP evaluator strongly maintains the position that these changes should be implemented prior to product approval.</p>
<p>It is recommended that the vial label for the 100 LD50 unit size vial be amended as follows. The proposed vial label for the 100 LD50 unit size vial reads: Xeomin 50 LD50 units powder for solution for injection (please refer to the copy of the label below, dotted arrow). This should be amended to: Xeomin 100 LD50 units powder for solution for injection</p>	<p>The vial label for the 100 LD50 unit size vial is amended and provided.</p>	<p>This is considered acceptable.</p>

Summary of recommendations

The introduced changes to the RMP do not address all the recommendations made in the first round RMP report and therefore, are considered to be insufficient.

At the time of preparation of this report it is recommended that EU-RMP, version 5.2, dated 6 September 2013 and Australian Specific Annex, dated October 2013, and any future updates be included as a condition of registration, if registration is approved.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Introduction

Xeomin is a highly purified, freeze dried formulation of botulinum neurotoxin type A that is free from complexing proteins.

The proposed indications are described below:

- Vertical 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. In subjects suffering from expression related GFLs due to muscle overactivity, facial lines in this area become static lines fixed in the skin at rest early in the aging process.
- Cervical dystonia is characterized 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.
- Blepharospasm is a progressive disease characterized by spontaneous, spasmodic, bilateral, intermittent or persistent involuntary contractions of the orbicularis oculi muscles.
- Spasticity is a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motor neuron syndrome. Only spasticity as a result of stroke and affecting the upper limbs in adults has been proposed as an indication for Xeomin. Broader spasticity indications apply to Botox.

Quality

There are no objections to approval of Xeomin on quality grounds.

IncobotulinumtoxinA (Purified neurotoxin free from complexing proteins) is synthesized from *Clostridium botulinum* as a single chain polypeptide with a molecular weight of approximately 150 kDa. On release from the organism the polypeptide is proteolytically processed into two subunits. The two subunits consist of a light chain (approximately 50 kDa) and a heavy chain (approximately 100 kDa) which are covalently linked via a disulfide bond.

Xeomin is supplied as a sterile, white, preservative free powder for solution for injection (lyophilisate) packed under nitrogen in glass vials. The vials are closed with rubber stoppers and aluminum caps. Each vial contains either 50 or 100 mouse LD50 units of

incobotulinumtoxinA (150 kD), 4.7 mg of sucrose and 1.0 mg of human serum albumin. Prior to use Xeomin is reconstituted with commercially available 0.9 % physiological saline (not supplied in the pack) to form a clear, and colourless solution. The size of the vials allows different concentrations (that is, doses) to be prepared. Reconstituted Xeomin is intended for intramuscular injection.

At the time of submission an International Non-proprietary Name (INN) for the drug substance has not yet been assigned. Following the ABN committee decision to adopt the ingredient name 'incobotulinumtoxinA' that matter is now resolved. In earlier documentation, including the letter of application and evaluation reports the name was referred to as Botulinum Toxin Type A (purified neurotoxin free of complexing proteins).

Nonclinical

There are no nonclinical objections to the registration of Xeomin for the proposed indications.

Adverse toxicological findings were consistent with the known class effects of Botulinum Toxin Type A and were mainly restricted to the injected muscle. There were no clinically relevant adverse local tolerance findings at less than or equal to 40 LDU/kg. Although the NOAEL for systemic toxicity corresponded to exposure levels only 1 to 2-fold higher than the maximum clinical exposure, there was no evidence that it differed in this respect from Botox and Dysport, which have been registered for therapeutic use in Australia for many years. In addition, adequate overseas clinical experience already available with Xeomin possibly mitigates the low exposure margins regarding potential systemic toxicity.

Although Xeomin is free of complexing proteins, antibodies can still be formed against the neurotoxin itself. Neutralising antibodies were not detected in 2 antigenicity studies in rabbits. The nonclinical evaluator referred this issue to the clinical evaluator to determine the potential for antibody formation in humans and noted that this is addressed in the Product Information and Risk Management Plan.

The pregnancy category of B3 has been recommended. This is consistent with the pregnancy category for other products containing Botulinum toxin type A.

Clinical

Pharmacology

No pharmacokinetic studies were submitted. Conventional pharmacokinetic studies cannot be performed with botulinum toxin in any of its forms, because it is extremely toxic when administered systemically. It is always administered locally, in very small quantities (picograms of toxin per injection), directly at the intended site of action or within a short distance of the intended target; it then spreads over a limited distance by local diffusion. The Xeomin preparation is no different to existing botulinum toxin preparations in this regard.

Xeomin and all Botulinum neurotoxins interfere with the release of acetylcholine (ACh) at the neuromuscular junction, thereby causing a neuromuscular paralysis, which is manifested as persistent, but not permanent, muscle relaxation. Recovery of endplate function/impulse transmission after intramuscular injection normally occurs within 3 to 4 months as nerve terminals sprout and reconnect with the muscle endplate and the presynaptic neurotransmitter release mechanism becomes functional again.

Three pharmacodynamic studies were included in the submission. Studies 9901 and 0113, described in the CER, investigated the effect of Xeomin on muscle activity in healthy

volunteers, as measured by the compound motor action potential (CMAP) in comparison to Botox. No clinically or statistically significant differences between the formulations were observed in these studies.

The third study (0709) assessed the effect of Xeomin on sweating by measuring the area of anhidrosis following an injection, in comparison to the commercial products Vistabel and Dysport. Doses of Xeomin, 5 U (incobotulinumtoxin A without complexing proteins); Vistabel, 5U (onabotulinumtoxinA, with complexing proteins); and Dysport 12.5 U (abobotulinumtoxinA) were administered in double-blind, randomised procedure.

Onabotulinumtoxin and abobotulinumtoxin are chemically distinct forms of the toxin, with slightly different molecular weights and different potencies. The dose of Dysport was considered equipotent to the Xeomin and Vistabel doses. The maximal area of anhidrosis after 6 weeks was compared between the three treatments. The area of anhidrosis served as an indicator of the diffusion characteristics of the different Botulinum toxin A products. Only descriptive statistics were provided. The area of anhidrosis was similar after Xeomin and Vistabel. For Dysport the area of anhidrosis was greater, indicating a greater area of diffusion in the forehead despite the fact that the Dysport dose (12.5 U) was intended to be comparable and the volume injected was identical. The clinical evaluator considered this may reflect the slightly lower molecular size of abobotulinumtoxin A compared to onabotulinumtoxinA.

Efficacy

There were 2 dose-finding studies: one in glabellar frown lines and the other in cervical dystonia. Given the pharmacodynamic evidence suggesting dose equivalence between Xeomin and Botox, the doses used in pivotal studies were either based on treatment guidelines developed for Botox, in the case of treatment-naïve subjects, or consisted of the patients' previous Botox dose.

Glabellar frown lines

Studies 0724 and 0721 were randomised, double-blind, placebo-controlled, multicentre studies to investigate the efficacy and safety of Xeomin in the treatment of glabellar frown lines. These studies were considered pivotal by the evaluator and are described in the CER. Another study (0520) had a similar design but not as robust a definition for clinical response and was considered supportive. Study 3002 was not double-blind and is also considered supportive. Those studies are described in the CER.

The pivotal studies had an identical design. Adult subjects with moderate to severe glabellar frown lines received 20 U Xeomin or matching placebo in a 2:1 ratio, injected as a single dose to five sites in the brow region and were followed for 120 days. The diagnosis of moderate to severe glabellar frown lines required a severity score of 2 or 3 on the Facial Wrinkle Scale. This scale was a four-point categorical scale based on the investigator's assessment of the severity of glabellar frown lines at maximum frown: "none" (0), "mild" (1), "moderate" (2), "severe" (3).

Subjects who had received Botulinum toxin within the previous 8 months were not eligible for inclusion in the studies.

The degree of facial/glabellar wrinkling was assessed by both physicians and subjects with both using 4-point scales of response. Physicians assessed the severity of glabellar frown lines at maximum frown using the Facial Wrinkle scale (FWS), a categorical scale based on the investigator's assessment of : "none" (0), "mild" (1), "moderate" (2), "severe" (3).

The subjects Patient's Assessment scale required responses to the following question which referred to their maximum frown: *'How would you judge the potency of frown muscle action by comparison to sample photos at this visit?'* Possible responses were:

- 0 = No muscle action at all;
- 1 = Some or slight muscle action possible that is, visible furrows;
- 2 = Moderately strong muscle action possible that is, visible muscle bulges;
- 3 = Strong muscle action possible which may cause local pallor.

The primary efficacy variable was a composite endpoint generated from the Facial Wrinkle scale (FWS) and the Patient's Assessment on a 4-point scale, in which subjects were considered treatment successes if they had at least a 2-point improvement in both physician and subject scales on Day 30 compared to Day 0. The primary efficacy variable was based on the FAS (all subjects who were randomised and treated with LOCF for missing data).

In Study 0724 a total of 276 subjects were randomised with 267 (97%) completing the study. Most subjects were female, aged less than or equal to 50 years (mean age 46.6 years) and white. Approximately a third had prior experience with Botulinum toxin. In the Xeomin group, 60.3% of subjects were CETS responders at Day 30 (95% CI: 0.52, 0.68; $p < 0.0001$), whereas no subject in the placebo group was a composite endpoint treatment success (CETS) responder. No placebo recipient showed a two-point response for either component of the CETS. Similar levels of response were seen for per-protocol analyses and observed case analyses. The various secondary efficacy analyses also strongly favoured the Xeomin group. Onset of treatment effect was apparent within 10 days of injection and responses tapered over the 120 review period with very few subjects showing a 2 point response at maximum frown by Day 120 post injection.

In Study 0741 a total of 271 subjects were randomised with 268 (99%) completing the study. As in Study 0724 the majority of subjects were white women aged less than or equal to 50 years (mean age 46.5 years). 19.2% had prior experience with Botulinum toxin. In the Xeomin group, 47.8% of subjects were CETS responders at Day 30 (95% CI: 0.40, 0.56; $p < 0.0001$) compared with none given placebo.

Data on maintenance of effect was obtained from Study 0609, an open, uncontrolled study which was ongoing at the time of submission. That study will include subjects who participated in the feeder studies: 0520, 0527, 0724, and 0741 but at the time of submission included only subjects from the supportive studies 0520 and 0527. Up to 8 treatment cycles are to be given. At the time of submission data on 35 subjects given 6 treatment cycles were available. No reduction in efficacy was apparent though data are limited in both duration and number of participants completing multiple treatment cycles.

Cervical dystonia

Four studies were submitted for this indication: a placebo-controlled, fixed dose study with open-label extension; an active-controlled, variable dose, non-inferiority study; a dose-finding study and open-post-market study to examine the duration of treatment effect.

Study 0408 was a 3-arm, double-blind, placebo-controlled, randomised, multicentre trial with a double-blind parallel-group extension period to investigate the efficacy and safety of different doses of Xeomin in the treatment of cervical dystonia. The main study period was 21 weeks for each patient and involved a single dose.¹⁵ Patients could enter an extension phase of up to 68 weeks, in which repeated doses were administered as needed. The efficacy and safety of Xeomin 240 U and 120 U were compared to placebo in the treatment of cervical dystonia in a mixed population of previously treated subjects and at least 40% treatment-naïve subjects.

¹⁵Sponsor clarification: 'In the Main Period of the study, subjects were followed for 8 to 20 weeks, until a new injection was required. Subjects could then continue to an extension phase of the study.'

Previous treatment with botulinum toxin was permitted, but had to have taken place at least 10 weeks earlier, and the therapeutic response had to have stabilised. The maximum dose of prior treatment was 300 units of type A toxin or 12000 units of type B toxin. Other treatments for dystonia had to be stable for at least 3 months prior to study entry. Subjects were randomised to one of the following treatments:

- 240 U of Xeomin in 4.8 mL sterile sodium chloride (NaCl) 0.9% solution;
- 120 U of Xeomin in 4.8 mL sterile NaCl 0.9% solution;
- placebo solution of the same volume (4.8 mL).

The number and sites of muscles to be injected were determined by the investigator. Doses were injected directly into the muscles thought to be responsible for the dystonia. The primary efficacy variable was change from baseline to Week 4 in the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS), a validated scoring system to assess the nature and severity of cervical dystonia. The primary analysis was of the ITT population with missing values replaced with the subject's baseline value. A total of 233 subjects were randomised, 81 to 240 U Xeomin, 78 to 120 U Xeomin and 74 to placebo. Statistically significant differences in the mean treatment difference between Xeomin 240 U group and placebo and Xeomin 120 U and placebo were seen for the overall populations and for the subgroups of Botulinum toxin experienced and naïve.

There was no statistically significant difference in mean change from baseline to Week 4 in the TWSTRS-Total score between groups given Xeomin 240 U and 120 U. The time to onset of subjective treatment effect was 6 to 7 days across all groups, even in the placebo group. Waning was noted after 7 to 8 weeks in the active groups. The duration of treatment effect, based on the time to re-treatment, was 10 to 12 weeks, similar to other studies.

Study 0013 was the second pivotal study for cervical dystonia. It was a double-blind, active (Botox) controlled study to show that a single dose of a Xeomin (individualised for each patient) was not inferior to a matching dose of Botox in the treatment of cervical dystonia, in terms of efficacy and safety. Patients were not eligible if they had received botulinum toxin preparations other than Botox in the last two treatments, or if they had undergone myotomy or previous denervation. All subjects received a dose of 70 to 300 U of NT 201 or Botox, diluted in normal saline, and administered intramuscularly to the neck muscles deemed responsible for the dystonia. The number and sites of injection was individualised, based on the patients' previous treatment with Botox. Subjects were then followed for up to 16 weeks.

As in Study 0408, the main efficacy variable was the TWSTRS score. The primary endpoint was the change in the TWSTRS-Severity subscore from baseline to the "control visit" at Day 28 plus/minus 3. The non-inferiority margin was 1.3 points in the TWSTRS scale. This margin was selected because it was half the observed placebo-difference (2.6 points) previously cited for TWSTRS-Severity scores in published literature. Of the 463 randomised subjects, 451 (97%) completed the study. At the Day 28 assessment both treatment groups had substantial and similar falls in mean TWSTRS-Severity scores. Mean reduction was 6.6 points from a baseline of 17.8 points in the Xeomin group and 6.4 points from a baseline of 17.7 points in the Botox group. In both groups, the changes compared to baseline were statistically significant ($p < 0.001$ by ANCOVA).

Non-inferiority of Xeomin to Botox was demonstrated for the Per-protocol population (primary analysis) with 95%CI: -1.05, 0.38 and for the ITT population. The time to subjective onset of treatment effect was very similar in the two treatment groups, and again ANCOVA did not detect any significant difference, as shown in the tables below. Onset of benefit, where noted, was typically 7 days after injection. Waning of effect was also similar with the two drugs, and typically occurred after 10 weeks

Follow-up data were available from Studies 0408/2 and 0605. Study 0408/2 was a double-blind extension of 0408. Subjects requiring re-treatment received either 240 U or 120 U Xeomin and could continue for up to 5 additional cycles which were to be at least 6 weeks apart. The same primary efficacy measures applied. A total of 86 subjects had received a 5th injection. There was little between group difference in efficacy for the 2 doses and efficacy compared with baseline was maintained in those subjects who continued to receive treatment. Study 0605 was an open, uncontrolled study in which subjects could receive up to 5 doses of Xeomin each up to 300 U.

Blepharospasm

Two pivotal studies were submitted, a placebo-controlled superiority study and an active (Botox) controlled non-inferiority study. Both were conducted in Botox experienced subjects.

Study 0433 was a double-blind, placebo-controlled, randomised, study with an open-label extension to investigate the safety and efficacy of Xeomin in comparison to placebo, when used to treat subjects with blepharospasm who had already been treated with Botox. Subjects were eligible if they were adults aged to 80 years, with a clinical diagnosis of benign essential blepharospasm (BEB), previously treated with Botox, and with a Jankovic Rating Scale (JRS) Severity subscore greater than or equal to 2 at baseline.

Subjects received either Xeomin or matching placebo in a 2:1 ratio. In the main study period subjects received a single treatment of up to 50 U per eye (mean total dose administered was 66.9 U). The dose was individualised per patient and was to be similar to the previous two injections prior to trial entry. The dose was distributed to up to 5 sites for each eye. In the open label extension subjects received up to 5 treatments with dose adjustment as needed consistent with standard clinical practice.

The JRS ranges from 0 to 8 points. It consists of two items (sub scores) "Severity" and "Frequency", with five rating categories each (0 to 4 points). It has been validated and its creator suggests that a change in the severity subscore of greater than or equal to 1 point is clinically meaningful. Reductions in JRS scores correspond to improvement.

The primary efficacy variable was defined as the change from baseline in the JRS Severity subscore (JRSSS, assessed by a blinded Independent Rater) at Visit 4 (Week 6 plus/minus 3 days) after injection. The JRSS ranges from possible values of 0 to 4. The primary analysis was of the ITT population.

A total of 108 subjects were randomised and received study medication (75 Xeomin, 34 Placebo) and 102 (94%) completed the double-blind phase of the study. In the Xeomin group, mean JRS Severity sub scores decreased from 3.12 points at baseline to 2.29 points at Week 6 (Visit 4). In the placebo group severity sub scores increased from 2.94 points to 3.15 points. Subjects receiving active treatment showed a mean improvement of 0.83 points, compared to a mean deterioration of 0.21 points in the placebo group. This was significant by ANCOVA ($p < 0.001$) with 95% CI (-1.4 to -0.5). In subjects given Xeomin the median time to maximal effect on JRS Severity was 5.5 weeks.

Study 0003 was a double-blind, randomised, active-controlled study to show that Xeomin was not worse than Botox in the treatment of blepharospasm, using doses up to 35 U per eye (70 U total per patient), in subjects previously treated with Botox. Subjects were eligible if they were adults aged up to 75 years, had BEB, had received Botox on at least two previous occasions and had shown a stable therapeutic response for the last two doses. A formal requirement for a specific severity of blepharospasm was not included in the inclusion or exclusion criteria. Subjects received a single dose of up to 35 U of Botox or Xeomin in each eye, matched to their previous stable dose of Botox. They were then followed for up to 16 weeks.

The primary efficacy variable was change from baseline in the JRS sum score, as assessed during a Control Visit on Day 21 plus or minus 1 day. The JRS was the rating scale used in the previous BEB study however the primary analysis was performed at Day 21 and the entire scale (frequency and severity) was included in the primary measure of efficacy. The primary analysis was performed on the per-protocol population. The mean difference between treatments for the primary efficacy variable was expressed as the least squares mean of the change from baseline for Xeomin, minus that for Botox. Non-inferiority was to be inferred if the 95% CI for the difference was < 0.8 points.

A total of 300 subjects were randomised with 256 included in the per-protocol population. The mean changes from baseline in JRS sum scores for each group at the Day 21 visit were similar (Xeomin -2.83 points; Botox -2.65 points) with a mean treatment difference in JRS of -0.2355 (95%CI: -0.6842 to 0.2191). Non-inferiority was also demonstrated at the final visit (up to Week 16). Mean time to onset of effect was approximately 1 week and mean duration of effect around 10 to 11 weeks.

Maintenance of effect was examined in the open-label extension to Study 0433. Subjects received up to 5 additional treatments of up to 50 U, given at least 6 weeks apart, with the interval depending on the response to previous treatment. A total of 56 subjects received 5 treatments with a continuing treatment response apparent.

Post-stroke spasticity of the upper limb

One pivotal study was performed with supportive data available from an extension to that study and from an uncontrolled study to examine the effect of 2 dilutions of Xeomin.

Study 0410 was a double-blind, placebo-controlled, randomised study, to investigate the efficacy and safety of individualised doses of Xeomin (170 U to 400 U) in comparison to placebo in the treatment of post-stroke spasticity of the upper limb, using a mixed population of botulinum-toxin naïve and pre-treated patients.

Major inclusion criteria were: post-stroke spasticity in a flexed wrist and clenched fist pattern, with both of the relevant muscle groups (wrist flexors and finger flexors) scoring greater than or equal to 2 in the Ashworth Spasticity Scale; that subjects had their last stroke greater than or equal to 6 months prior to study screening; and the Botox not have been administered within 4 months prior to screening. Subjects received a single treatment Xeomin or placebo of between 170 U (3.4 mL trial medication) and 400 U (8.0 mL) using the following injection volumes and distribution:

Table 6. Doses for clinical patterns that had to be treated in each patient at baseline visit (flexed wrist and clenched fist) of the main period

Clinical Pattern	Muscles for Treatment	Units NT 201	Calculated Volume (NT 201 or Placebo)	Number of Injection Sites
Flexed Wrist	<i>flexor carpi radialis</i>	50	1.0 mL	2
	<i>flexor carpi ulnaris</i>	40	0.8 mL	2
Clenched Fist	<i>flexor digitorum superficialis</i> ¹	40	0.8 mL	2
	<i>flexor digitorum profundus</i> ¹	40	0.8 mL	2

Clinical Pattern	Potential Muscles for Treatment	Units NT 201	Calculated Volume (each dose group)	Number of Injection Sites
Flexed Elbow*	<i>brachioradialis</i>	60	1.2 mL	1-3
	<i>biceps</i>	80	1.6 mL	2-4
	<i>brachialis</i>	50	1.0 mL	1-2
Pronated Forearm	<i>pronator quadratus</i>	25	0.5 mL	1
	<i>pronator teres</i>	40 [#]	0.8 mL	1-2
Thumb-in-Palm	<i>flexor pollicis longus</i>	20	0.4 mL	1
	<i>adductor pollicis</i>	10	0.2 mL	1
	<i>flexor pollicis brevis / opponens</i>	10	0.2 mL	1

* All patients with a clinical pattern of Flexed Elbow had to be treated in the biceps muscle and in at least one of the two other elbow flexors: brachioradialis and / or brachialis

WE MOVE originally recommended 40 to 50 units BOTOX[®].

Subjects then were then followed for 13 -21weeks before switching to an open-label extension study. The Ashworth scale is a validated 5-point scale for assessment of spasticity with 0 = no tone and 4 = limb rigid in flexion or extension. The primary efficacy variable was the response rate at Week 4, with response defined as an improvement (reduction) of at least 1 point from the Baseline Visit (Day 0) in the Ashworth Scale score for wrist flexors. The primary analysis for efficacy was of the ITT population (observed cases).

A total of 148 subjects were randomised (73 to Xeomin; 75 to placebo) with 145 (98%) completing the initial double-blind treatment period. Most (64.2%) subjects were male, mean age was 55.6 years and 24.3% of subjects had received prior Botox for spasticity of the upper limb. The mean time since the most recent stroke was 56.45 months (Range: 5.91 to 261.0 months). The mean dose of Xeomin was 306.9 U. A total of 50 (68.5%) subjects given Xeomin and 28 (37.3%) given placebo were 1-point responders on the Ashworth scale. The OR in the full statistical model was 3.97 (95%CI: 1.81 to 7.06; p<0.001).

Statistically significant differences in the OR for response between the Xeomin and placebo groups were generally seen until Week 8 of the double-blind period however, as shown in Table 35 in the CER median time to waning of the treatment effect was 10 weeks. Onset of effect was generally apparent within 4 days of treatment. Injections could be repeated at the Week 12 visit.

Study 0607 was a randomised, observer-blind study to assess the efficacy and safety of 2 dilutions of Xeomin in subjects with upper limb spasticity. The primary objective was to show non-inferiority of an injection of Xeomin high-volume dilution (20 U/mL) compared to Xeomin low-volume dilution (50 U/mL). This study included patients with a variety of causes for their spasticity, rather than just post-stroke spasticity. It sought to demonstrate

that the Xeomin has similar efficacy across a range of dilutions. This demonstration was considered necessary because the dilution of botulinum toxin is usually variable and individualised, depending on the site and indication. In Study 0410 only the low volume (50 U/mL) dilution was used. If it was necessary to treat additional muscles, that is Ashworth scale greater than or equal to 1, this was done at the discretion of the investigator using the WE MOVE recommendations as long as the total dose per injection session was less than or equal to 400 units Xeomin. The injection sites and doses were similar to those of Study 0410.

This study used a different primary efficacy endpoint, based on the Disability Assessment Scale at Week 4. The non-inferiority margin was taken as 0.25 on the 4-point DAS. Non-inferiority of the high volume (20 U/mL) solution with the low volume (50 U/mL) Xeomin solution was demonstrated. The DAS response rate for the 20 U/mL solution was trended higher than that of the 50 U/mL solution but statistically significant superiority was not demonstrated. On this basis, the two dilutions should be considered equivalent in terms of efficacy.

Maintenance of effect was examined in the extension to Study 0410 in which all subjects received Xeomin, with the maximum dose administered 500 U. Doses were individualised, but were based on standard recommendations for the treatment of post-stroke spasticity. Only 16 subjects had received 5 treatments however 80 had received 4 treatments and an ongoing treatment effect was apparent. No reduction in dose interval was seen during the open-label period.

Safety

The major safety concerns with Botulinum toxins A are paralysis in unintended sites either adjacent to or distant from the site of injection and the development of immune reactions to the injected product. The immunogenicity of Xeomin can be considered in two contexts: the development of neutralising antibodies, which potentially compromises the efficacy of the toxin, and the occurrence of clinically significant allergic reactions.

In this clinical program a total of 2,068 subjects were treated with Xeomin in single-dose studies, and 1,313 of these also entered repeated-dose studies. More than half of these (1,067) received Xeomin for GFL, and therefore received a low dose (range 10 to 30 U). Higher doses were tested in the cervical dystonia population (n = 431, median dose 120 U) and in the treatment of upper limb spasticity (n = 265, median dose 300 U). A total of 79 patients, all with upper limb spasticity, received doses of greater than 360 U. 206 subjects received 8 injections, all were treated for glabellar frown lines.

The TEAEs that showed an excess in the Xeomin group included: headache, musculoskeletal disorders (including neck pain, back pain and musculoskeletal pain, and weakness), gastrointestinal disorders (including dysphagia), oropharyngeal pain, eyelid ptosis and dry eye. For most of these, a plausible causal relation between active treatment and the TEAE can be envisaged, particularly TEAEs that involve weakness (ptosis, dysphagia) or impairment of secretions (dry eye, dry mouth). As noted by the evaluator, overall the incidence of AEs was similar with Xeomin and other botulinum toxin A preparations, as would be expected given that Botox can be considered a pro-drug for Xeomin, and dissociates soon after injection to release purified toxin identical to Xeomin. There were no control groups for the repeat dose studies so it is not possible to determine from direct comparisons whether Xeomin has a different side effect profile from other botulinum toxin A products.

Six deaths were reported in the clinical development program. None were attributed to treatment with Xeomin.

In subjects enrolled in the single dose studies who were botulinum antibody negative at study commencement neutralizing antibodies occurred in 0.7% of subjects given Botox

(0.7%) and in 0.4% given Xeomin. This analysis was not adequately powered for a statistical comparison. Neutralising antibodies did not develop in the placebo group.

Various AEs consistent with allergic reactions occurred in clinical trials but have not been attributed to study treatment. These include: rash, urticaria, conjunctivitis, dermatitis contact and hypersensitivity. It is not clear why these events were not considered related to Xeomin.

The sponsor has advised that “local allergic reactions and flu-like symptoms” have emerged as a safety signal during post-marketing surveillance. The nature and strength of this safety signal was not discussed in the submission. The sponsor is requested to provide further information on this safety signal.

Risk management plan

Negotiation of the final RMP is ongoing. The RMP evaluator has recommended that the requirements of EU-RMP, version 5.2, dated 6 September 2013 and Australian Specific Annex, dated October 2013, and any future updates be adopted as a condition of registration.

The RMP evaluator had recommended disclosure of the limited safety information for patients aged over 55 years and over 60 years. The sponsor subsequently provided information on the extent of safety information from patients in those age groups. Data from 629 patients aged greater than 50 to 65 years were analysed. The percentage of patients with TESAEs (treatment emergent serious adverse events) in this age group is comparable to the age group less than or equal to 50 years (1.9% versus 1.7%). The incidence of common and very common adverse events the age groups were comparable (less than or equal to 50 years = 45.8%; greater than 50-65 years = 46.7%).

Patients from 60 to 65 years (n = 316) were included in the analysis of the 629 patients greater than 50-65 years but have not been analysed separately. The sponsor has agreed to analyse these data separately.

Risk-benefit analysis

Delegate’s considerations

Xeomin contains the same active component as Botox as thus could be assumed to have equal potency however it is not considered that this has been adequately demonstrated in the clinical trial program presented and at this stage do not intend to allow that claim to be made in the PI for Xeomin. The initial doses and dose intervals have been based on the dose regimens for the various indications for Botox and while appropriate clinical trials for the proposed indications were performed there was no exploration of alternative dosing intervals. Given the duration of effect was monitored in the studies the Delegate has no objection to the proposed dose intervals, however a recommendation for minimal effective dosing should be emphasised as requested in the attached PI review.

No new safety issues with Xeomin compared to the known safety profile of other products containing botulinum toxin was apparent. Whether allergies and the development of neutralising antibody will be less of a concern with Xeomin compared with other botulinum toxin products has not been determined.

Glabellar frown lines (GFL)

Acceptable efficacy, with a response rate of around 60% at Day 30 post injection was demonstrated for this indication. The dose regimen used in the pivotal clinical trials was 20U distributed in 5 injections to the brow region. The sponsor is proposing total doses of

up to 30U for this indication. The sponsor is also claiming the maximum effect is on Day 30 post treatment and that the effect lasts up to 4 months. The clinical evaluator noted that Xeomin appears to produce its maximal effect in the first week, show persistence of efficacy for the first month, and then begin to wane in efficacy by the second and third month. However the response rate was highest at Week 4, substantiating the claimed timing of maximum effect. Very few subjects had responses at Day 120. It is unclear whether the effect will continue to last for the same duration or whether the extent of effect will wane with further doses because the long term maintenance study has not been completed.

Cervical dystonia

Acceptable efficacy was also demonstrated for Xeomin for this indication. The doses used in the pivotal trials were 120U and 240 U. No significant difference in effectiveness between the doses was demonstrated. The sponsor proposes to recommend that normally the total dose should not exceed 200 U per treatment session but that doses of up to 300 U may be given and that no more than 50 U should be given at any one injection site. The sponsor is required to justify the proposed dosing instructions given the lack of demonstrated increased efficacy for doses above 120 U. The proposed dosing intervals of at least 6 weeks were supported by the extension study.

Blepharospasm

The pivotal studies for this indication were a placebo-controlled study and a non-inferiority study where Botox was the comparator. In the latter study the non-inferiority margin was quite broad with a difference of up to 0.8 on the JRS scale considered a non-clinically significant difference. The mean difference from placebo in the placebo-controlled study at the primary efficacy time point was 1.04 on the JSR scale, so a narrowed difference of say 0.5 on the JRS scale would have better demonstrated the non-inferiority of the two treatments. Nevertheless adequate efficacy has been demonstrated for the dose regimen used in the pivotal studies.

The sponsor has proposed an initial recommended dose of 1.25 to 2.5 U (0.05-0.1 mL volume)/injection site with the same injection sites as in the pivotal studies. The recommendation that the initial dose should not exceed 35 U/eye for pre-treated patients if the previous dose of Botulinum toxin is not known and the total dose no more than 100U (that is, 50 U per eye) is supported by the studies. The proposal that treatment be repeated no more frequently than 6 weekly was supported by the maintenance study in this indication.

Post-stroke spasticity of the upper limb

The sponsor is proposing the same dose regimens and injection sites for spasticity involving flexed wrists and elbows, clenched fist, pronated forearm and thumb in palm as were given in the clinical trials for this indication. Efficacy was adequately demonstrated. The effect began to wane around Week 10, supporting the proposed minimum dose interval of 12 weeks.

Summary of issues

- The indication for glabellar frown lines specifically excludes adults aged less than 65 years. This appears unnecessarily restrictive.
- Maximum doses higher than those given in pivotal clinical trials have been proposed for glabellar frown lines and cervical dystonia.
- Repeat dose intervals do not appear to have been independently established.
- The sponsor is proposing to include the following statement in the DOSAGE AND ADMINISTRATION section of the PI: Comparative clinical study results suggest that

Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used in a dose conversion ratio of 1:1. The acceptability of this statement is uncertain.

Proposed action

There is no reason to say, at this time, that the application for Xeomin should not be approved for registration.

Request for ACPM advice

The Committee is requested to provide advice on the following specific issues:

- Should the upper age limit for the glabellar frown line indication be removed?
- Given that for cervical dystonia the 120 U total dose resulted in improvements that were not statistically significantly different from the 240 U dose, is the proposed maximum dose of 300 U for this indication adequately supported by data?
- Given that for GFL the maximum dose given in pivotal clinical trials for this indication was 20 U is it appropriate that the maximum recommended dose for this indication be 30 U as proposed by the sponsor.
- In general the repeat dosing intervals recommended for Xeomin have been modelled on those of Botox. Does the committee consider this is appropriate or should alternative repeat dose intervals have been explored?
- Is the extent of equivalence demonstrated in the comparative clinical trials adequate to justify the proposed statement regarding equal potency of Xeomin and conventional Botulinum toxin type A complex?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Indication

- The indication for glabellar frown lines specifically excludes adults aged < 65 years. This appears unnecessarily restrictive.

Response:

While the text above (as extracted from the Delegate's Summary of Issues) includes the 'less than' symbol, it is clear to the sponsor that this is an error and should be a 'greater than' symbol. The following response is based on the symbol being 'greater than'.

Merz agrees that excluding the treatment of patients greater than 65 years is unnecessarily restrictive and not justified. Subjects in the age of 65 years or older have been treated in all pivotal trials. No differences in efficacy and safety between patients below and above 65 years have been observed based on these study data. From a physiological and clinical perspective an increased safety risk in elderly patients is not expected.

Dosage

- Maximum doses higher than those given in pivotal clinical trials have been proposed for glabellar frown lines and cervical dystonia.

*Response:**Glabellar Frown Lines:*

The recommended standard dose of 20 units will be appropriate for the majority of patients. However, from a clinical point of view a higher dose may be required especially in patients with a higher muscle mass (for example, male patients).¹⁶ Safety and efficacy of GFL treatment with 30 units have been demonstrated in the Phase II study MRZ-0527. Therefore, the dose may be increased by the physician to up to 30 units if required by the individual needs of the patients. The DOSAGE AND ADMINISTRATION section of the PI information was revised to reflect this information. The proposed recommended standard and maximum dose for GFL (that is, 20 to 30 units) is approved in the European Product Information Texts of Bocouture (for example, in United Kingdom, Sweden and The Netherlands).

Cervical Dystonia:

Dosing recommendations for treatment of cervical dystonia which are proposed for Xeomin in Australia are consistent with dosing recommendations approved in the countries of the European Union. They are based on the results of active-comparator controlled pivotal Study MRZ-0013 conducted in Europe and Israel and published in Neurology.¹⁷ Merz believes that this study, which allowed for flexible dosing in accordance with individual patients' needs (as a function of the number of muscles affected and of the degree of spasticity in each individual muscle) was designed much closer to clinical reality than the US pivotal Study MRZ-0408,¹⁸ in which fixed doses of either 120 U or 240 U had to be administered without the ability to adapt to individual patient needs. The authors of the study results publication themselves saw this as an important limitation: *'The fixed dosages are also one of the limitations of the study in that no dosing flexibility was permitted in order to optimize therapy'*,¹⁹ reporting the open-label extension period (EP) results of the US pivotal study, further commented: *'Neither the MP (Main Period) nor the EP was designed or powered to identify differences between the two dose groups and, accordingly, statistical analyses of treatment differences between the dose groups did not reach significance. To meet the requirements specified by regulatory authorities, subjects in this trial received randomized, fixed doses of incobotulinumtoxinA. Thus, total doses were not based on individual subjects' medical needs and condition and did not take into consideration any previous botulinum toxin treatment outcomes subjects may have experienced, as would be standard practice in the treatment of CD outside a clinical trial setting.'*

Although the study could not demonstrate superiority of the 240 U dose over the 120 U dose, both doses were shown to be superior to placebo, and there was a nominal trend in favour of the higher dose over the lower dose.

Study MRZ-0013 illustrates that while the median dose of Xeomin was 120 U, 25% of patients received between 186 and 300 U of Xeomin, thus including the proposed maximum dose for this indication. In the same study, 25% of the patients in the Botox arm received doses between 180 and 280 U. This reflects that Xeomin is used at similar doses as Botox, and given the similarity of efficacy results seen in the same study for the two comparator products; this also supports the use of Xeomin at the same doses as those used for Botox.

¹⁶ Carruthers J et al, Consensus recommendations on the use of botulinum toxin Type A in facial aesthetics, 2004.

¹⁷ Benecke R et al, A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia, Neurology, 2005; 64: 1949-1951.

¹⁸ Comella C et al, Efficacy and safety of incobotulinumtoxinA (NT 201, Xeomin, botulinum neurotoxin type A, without accessory proteins) in patients with cervical dystonia, Journal of the Neurological Sciences, 2011.

¹⁹ Evidente V et al, A randomized, double-blind study of repeated incobotulinumtoxinA (Xeomin) in cervical dystonia, J Neural Transm, 2013.

The use of Xeomin in doses higher than 240 U in treatment of cervical dystonia is further supported by a recent publication,²⁰ Dressler et al report on open-label long-term treatment of 40 patients who were converted from Botox to Xeomin in a 1:1 ratio. The average dose applied per injection session was 296 U.

The current US PI for Botox states with regard to the pivotal US efficacy study in CD: '*In this study the median total Botox dose in patients randomized to receive Botox (n = 88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units.*' Interestingly, no maximum dose specific to cervical dystonia is recommended in the US PI. Instead there is a general statement on maximal dose across all indications:

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should generally not exceed 360 Units, in a 3 month interval and a specific statement on initial dosing in CD: Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of Botox should be at a lower dose, with subsequent dosing adjusted based on individual response.

The current European SmPC of Botox similarly states with regard to the cervical dystonia dosing: '*In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of reconstituted Botox ranged from 140 to 280 Units. In more recent studies, the doses have ranged from 95 to 360 Units (with an approximate mean of 240 Units). As with any drug treatment, initial dosing in a naïve patient should begin at the lowest effective dose. No more than 50 Units should be given at any one injection site. No more than 100 Units should be given to the sternomastoid. To minimise the incidence of dysphagia, the sternomastoid should not be injected bilaterally. No more than 200 Units total should be injected for the first course of therapy, with adjustments made in subsequent courses dependent on the initial response. A total dose of 300 Units at any one sitting should not be exceeded.*'

Finally, the current Australian product information for Botox (dated 06 August 2013), provides the following specific dosing information for cervical dystonia: '*In initial controlled clinical trials to establish safety and efficacy for cervical dystonia, doses of Botox ranged from 140 to 280 U. In more recent studies, the doses have ranged from 95 to 360 U (with an approximate mean of 240 U). As with any drug treatment, initial dosing should begin at the lowest effective dose. In general, a total dose of 360 U every two months should not be exceeded for the treatment of cervical dystonia.*'

Merz believes that therapeutic equivalence can be concluded between Xeomin and Botox in the treatment of CD (please see our response to topic 4), and as such the dosing recommendations proposed for Xeomin should be aligned with approved dosing recommendations for Botox. Furthermore, dosing up to 300 U is supported independently by Study MRZ-0013 and additional published data. This maximum dose will allow the physician to tailor the treatment to the individual patient's need also in severely affected subjects.

- Repeat dose intervals do not appear to have been independently established.

Response:

As has been stated by the Delegate, the proposed dosing intervals of at least 6 weeks for Xeomin in cervical dystonia '*were supported by the extension study,*' and not only by

²⁰ Dressler D et al, Botulinum toxin therapy of cervical dystonia: comparing onabotulinumtoxinA (Botox) and incobotulinumtoxinA (Xeomin), J Neural Transm, 2013a

reference to Botox. The results of the extension study have recently been published in a peer-reviewed journal.²¹ The authors concluded that *'repeated incobotulinumtoxinA injections (240 or 120 U; flexible intervals) provided sustained efficacy and were well tolerated, with no unexpected safety risks following repeated injections'* and that *'no additional safety concerns were observed in subjects who received injection sessions at short intervals (6 to \leq 10 or $>$ 10 to \leq 12 weeks) compared with those who received injection sessions at longer intervals ($>$ 12 weeks).'*

For blepharospasm, similar conclusions were drawn²² in their recent publication on the results of the respective extension trial: *'Repeated incobotulinumtoxinA injections, administered at flexible doses and injection intervals from 6 to 20 weeks according to subjects' needs, provide sustained efficacy in the treatment of blepharospasm with no new or unexpected safety risks.'*

Merz thus believes that repeat dose intervals of at least 6 weeks have been independently established for Xeomin for both cervical dystonia and blepharospasm.

- The sponsor is proposing to include the following statement in the DOSAGE AND ADMINISTRATION section of the PI: Comparative clinical study results suggest that Xeomin and the comparator product containing conventional Botulinum toxin type A complex (900 kD) are of equal potency when used in a dose conversion ratio of 1:1. The acceptability of this statement is uncertain. Committee members are requested to consider the Minutes from item 3.1 from the 218th ADEC meeting.

Response:

Non-inferiority of Xeomin/Bocouture efficacy as compared to a comparator product Botox/Vistabel was shown in one comparative single-dosing Phase III study in patients with GFL (MRZ-GL3002, n = 381). Both products showed a similar efficacy and safety profile.

Furthermore, Studies MRZ-0003 in blepharospasm and MRZ-0013 in cervical dystonia were active-controlled, non-inferiority studies comparing Xeomin against onabotulinumtoxinA (Botox, Allergan) administered in equal doses. Both studies pre-specified the 2-sided 95% confidence interval (CI) method for testing not only non-inferiority but also therapeutic equivalence of Xeomin versus Botox, based on an analysis of covariance (ANCOVA) model.²³ In the blepharospasm study the primary efficacy variable was the change from baseline in Jankovic Rating Scale (JRS) sum score to 3 weeks post injection and the ANCOVA model included treatment group, baseline JRS sum score, pooled country, and dose as factors or covariates. Non-inferiority was concluded because the upper confidence limit was below the pre-defined non-inferiority margin $\Delta = 0.8$. In the cervical dystonia study the change from baseline in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) Severity score to 4 weeks post injection was the primary efficacy variable and treatment group, baseline TWSTRS Severity score, country, gender and age were included in the ANCOVA model as factors or covariates. Non-inferiority in this study was concluded because the upper confidence limit was below the clinically irrelevant difference $\Delta = 1.3$.

In addition, therapeutic equivalence could be deduced from a statistical conclusion based on the closed test procedure, which implies that if non-inferiority was demonstrated, then superiority and equivalence can be shown without further adjustment of type I error.

²¹ Evidente V et al, A randomized, double-blind study of repeated incobotulinumtoxinA (Xeomin) in cervical dystonia, J Neural Trans, 2013

²² Truong D et al, Sustained efficacy and safety of repeated incobotulinumtoxinA (Xeomin) injections in blepharospasm, J Neural Transm, 2013

²³ Roggenkämper and Hauschke 2012, Benecke and Hauschke 2012

In terms of testing for superiority of any product, the 95% CI included 0, indicating that the mean changes in JRS Sum score and TWSTRS Severity score, respectively, were not statistically different between the products.

In contrast, therapeutic equivalence could be concluded in both studies as the following conditions were fulfilled: The protocols pre-specified the non-inferiority margin by a clinically irrelevant difference, thereby defining not only a non-inferiority margin but also an equivalence range, that is, (- 0.8; + 0.8) in case of the blepharospasm study and (- 1.3; + 1.3) in case of the cervical dystonia study. The protocols pre-specified a 2-sided 95% confidence interval as method for analysis, and for both studies this confidence interval was completely covered by the predefined equivalence range - Δ and + Δ . For the blepharospasm study the least square means difference (95% CI) between Xeomin and Botox was -0.23 (-0.68; 0.22). For the cervical dystonia study the corresponding results were -0.33 (-1.05; 0.38).

Merz thus believes that these results of both studies and further published data²⁴ support the statement of *'equal potency of Xeomin and Botox when used in a dose conversion ratio of 1:1.'*

Safety

- The sponsor has advised that *'local allergic reactions and flu-like symptoms'* have emerged as a safety signal during post-marketing surveillance. The nature and strength of this safety signal was not discussed in the submission. The sponsor is requested to provide further information on this safety signal.

Response:

Based on monthly regular signal detection, signal evaluations were performed concerning allergic reactions/hypersensitivity reactions (2009 and 2012) and flu-like symptoms (2012). A signal for localised allergic reactions was confirmed based on the evaluation performed in 2009. A signal for hypersensitivity reactions (generalised) and for flu-like symptoms was confirmed following the signal evaluations in 2012. Therefore hypersensitivity reactions (including detailed description of symptoms) and flu-like symptoms were added to the post-marketing section of the applicant's company core data sheet of Xeomin and should also be included in the Australian PI of Xeomin.

A summary of the evaluation reports is described below:

The first signal evaluation of hypersensitivity reactions identified sixteen cases which mostly described local allergic reactions manifesting in symptoms like oedema and redness. Generalised hypersensitivity reactions have been described in at least six cases reported from post-marketing experience. They are manifesting in generalised skin reactions, in one case accompanied with Quincke's oedema, in two cases each accompanied with breathlessness and/or dysphagia. All events were non serious. All cases were assessed as possibly or probably related by the applicant and as related, probably or possibly related by the reporter. The reactions occurred independent from indication.

In the scientific literature only very few cases of generalised hypersensitivity reactions have been described.

On request of the German Authority, BfArM, hypersensitivity reactions are presented as identified risk in the EU Risk Management Plan for Xeomin and are therefore closely monitored.

Based on the above mentioned facts Merz proposes to include hypersensitivity reactions (PT hypersensitivity) like swelling, oedema, erythema, pruritus, rash and breathlessness

²⁴ Dressler D et al, Botulinum toxin therapy of cervical dystonia: comparing onabotulinumtoxinA (Botox) and incobotulinumtoxinA (Xeomin), J Neural Transm, 2013a

(PT dyspnoe) in the post-marketing experience section in of all labelling documents for Xeomin including the Australian PI.

The applicant's safety data base was searched for flu-like symptoms referring to symptoms as defined by the coordination centre EURO FLU of the WHO. Some but not all of these symptoms have been observed in the course of the reaction to Xeomin. The systematic search in the applicant's safety database identified six spontaneous reports describing flu-like symptoms. Five of these reports were assessed as possibly related to Xeomin, and one was not assessable due to insufficient information. A further four reports could also be considered as describing 'flu-like symptoms' based on the description of the events. Two were assessed as possibly related and two were not assessable due to insufficient information. The most frequent symptoms were muscle aches, fatigue, general malaise, asthenia, which were summarised as flu-like symptoms in some reports. The symptoms were not associated with the indication for use or with the dose of Xeomin administered.

The evaluation of the applicant's clinical database revealed that adverse reaction terms pointing to flu-like symptoms tended to be seen more often under treatment with Xeomin than under placebo.

A systematic literature search revealed at least 23 articles where flu-like symptoms are explicitly described as drug reactions to botulinum toxin A. Flu-like symptoms are also mentioned as adverse reactions in the prescribing information for other botulinum toxin products. Based on the evaluation of the systematic search in the applicants safety database, clinical database, on the scientific literature, and on the package inserts of other botulinum products, a causal relationship between the use of Xeomin and the event "flu-like symptoms" could be concluded. This adverse effect appears to be independent of the toxin dose and the indication being treated.

Merz thus proposed to add the term "Flu-like-symptoms" in the post-market experience section to all labelling documents of Xeomin including the Australian Xeomin PI.

RMP Evaluation

- Patients from 60-65 years (n = 316) were included in the analysis of the 629 patients > 50-65 years but have not been analysed separately. The sponsor has agreed to analyse these data separately.

Response:

The sponsor has completed the analysis described above, the results of which are provided to TGA.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Xeomin Powder for injection containing 50 LD50 units and 100 LD50 units of botulinum toxin - type A to have an overall positive benefit-risk profile for the amended indication;

Xeomin is indicated for use for the treatment of:

- Glabellar frown lines in adults
- Cervical dystonia in adults

- Blepharospasm in adults
- Post-stroke spasticity of the upper limb in adults

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Specific advice:

- Should the upper age limit for the glabellar frown line indication be removed?

The ACPM agreed with the Delegate and noted that the sponsor had also agreed that the upper age restriction was unnecessary.

- Given that for cervical dystonia the 120 U total dose resulted in improvements that were not statistically significantly different from the 240 U dose, is the proposed maximum dose of 300 U for this indication adequately supported by data?

The ACPM was of the view that the evidence did not support use of this dose; however its use is possible on the basis of experience with Botox.

- Given that for GFL the maximum dose given in pivotal clinical trials for this indication was 20 U is it appropriate that the maximum recommended dose for this indication be 30 U as proposed by the sponsor.

The ACPM advised that the validity of this dose supported by submitted data and experience with Botox.

- In general the repeat dosing intervals recommended for Xeomin have been modelled on those of Botox. Does the committee consider this is appropriate or should alternative repeat dose intervals have been explored?

The ACPM advised repeat dosing is straightforward to determine in individual patients and dose intervals are supported by the submitted data.

- Is the extent of equivalence demonstrated in the comparative clinical trials adequate to justify the proposed statement regarding equal potency of Xeomin and conventional botulinum toxin type A complex?

The ACPM was of the view that there was insufficient evidence to support the use of the specific word “potency”, although equivalence of effect was suggested by the data.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of

- Xeomin incobotulinumtoxinA, 100 LD50 units; purified neurotoxin, free from complexing proteins and
- Xeomin incobotulinumtoxinA, 50 LD50 units; purified neurotoxin, free from complexing proteins

indicated for:

- *Cervical dystonia in adults*
- *Blepharospasm in adults*
- *Post-stroke spasticity of the upper limb in adults*
- *Glabellar frown lines in adults*

The dosage of Xeomin will be individualised according to indication and individual patient.

Specific conditions of registration applying to these goods

1. Implementation in Australia of the Xeomin, incobotulinumtoxinA EU- Risk Management Plan (amp), version 5.2, dated 6 September 2003 and the Australian Specific Annex, dated February 2014, included with submission 2012-04159-1-1, and any future updates, as agreed with the TGA's Office of Product Review.
2. Furthermore, any commitments made by the sponsor and as agreed by OPR in the post-M3 response (2 October 2003), post M5 response (16 December 2013), response to TGA request for additional RMP information (dated 7 February 2014) and amendment to response #4 (e-mail dated 18 February 2014), must be fulfilled.

Attachment 1. Product Information

The Product Information approved for Xeomin at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
<http://www.tga.gov.au>