

# Recent Advances in the Treatment of Focal Dystonia: Update from the Dystonia Europe 2008 conference

The Dystonia Europe 2008 conference (October 17–19 in Hamburg, Germany) was the first major meeting for over 10 years with an exclusive focus on dystonia. It brought together experts from Europe and North America to discuss the latest developments in clinical practice and research.

The conference included a number of posters reviewing the latest findings from an extensive clinical development programme for Xeomin® in the treatment of focal dystonia. Xeomin® is a new formulation of botulinum neurotoxin type A that has recently been launched in the UK. Unlike existing therapies, Xeomin® is free from complexing proteins and can be stored at room temperature (<25°C) prior to reconstitution.<sup>1</sup>

The posters presented data demonstrating that Xeomin® is effective and well tolerated in the treatment of cervical dystonia and blepharospasm<sup>2-4</sup> and challenged the concept that complexing proteins may play a positive role in the stability and diffusion of botulinum toxin once injected.<sup>5</sup>

## Comparable outcomes of Xeomin® (Botulinum neurotoxin type A) and Botox® in the treatment of focal dystonia

The results from two key studies were combined in a pooled analysis by Professor Jost from the Deutsche Klinik für Diagnostik in Wiesbaden, Germany.<sup>2</sup> The studies represented the two largest, randomised, double-blind, active-controlled clinical trials of botulinum neurotoxin conducted in patients with spasmodic torticollis<sup>6</sup> or blepharospasm.<sup>7</sup>

In both studies, patients with a stable therapeutic response to Botox® were randomised to either maintain their existing Botox® dose or be switched to a matched dose of Xeomin®. Due to the differences in LD<sub>50</sub> assays used by different manufacturers, unit doses are specific to individual products and are not interchangeable. In these studies a conversion factor of 1:1 was used, such that if a patient was stable on 100 (Allergan) units of Botox® they were switched to 100 (Merz) units of Xeomin®. In the two studies a total of 384 patients received Botox® and 379 patients received Xeomin®.

In this combined analysis, Xeomin® was found to be equally as efficacious as Botox® across a number of physician and patient assessed parameters.<sup>2</sup>

- 72.8% of the investigators rated Xeomin® as 'good' or 'very good' (compared with 68.4% for Botox®) (Figure 1).

- 76.6% of patients indicated a moderate or marked improvement – including the complete abolition of symptoms – with Xeomin® treatment (compared with 72.0% with Botox® treatment) (Figure 2).

- 89.6% of patients indicated they had improved with Xeomin® treatment (compared with 85.8% with Botox® treatment) (Figure 2).

- The duration of treatment effect was almost identical in each treatment group (110 days with Xeomin® and 111 days with Botox®).

- The efficacy of Xeomin® and Botox® were shown to be statistically comparable.

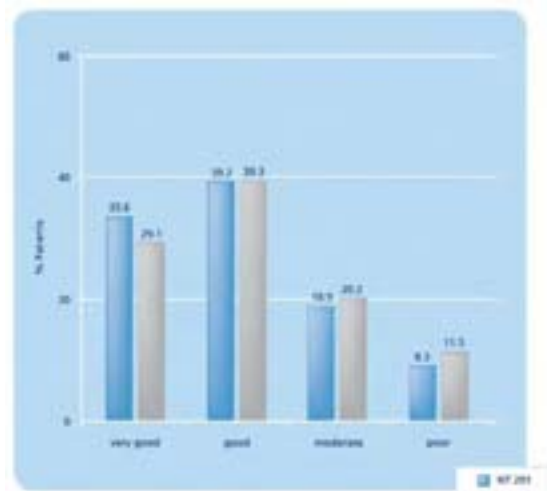


Figure 1: Investigators' global assessment of the efficacy of Xeomin® (NT 201) and Botox® (BTXCo) in focal dystonia (intention to treat analysis)<sup>2</sup>

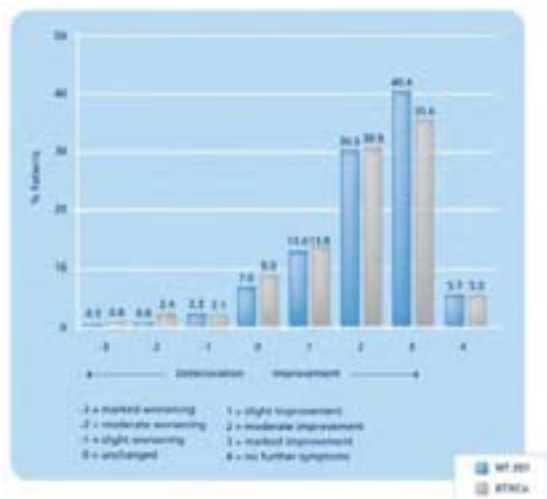


Figure 2: Patients' global assessment of the efficacy of Xeomin® (NT 201) and Botox® (BTXCo) in focal dystonia (intention to treat analysis)<sup>2</sup>

### XEOMIN® Abbreviated Prescribing Information.

Please refer to Summary of Product Characteristics before prescribing.

**Presentation:** 100 LD<sub>50</sub> units of Clostridium Botulinum neurotoxin type A (150 kD), free from complexing proteins, as a powder for solution for injection.

**Indications:** Symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults.

**Dosage and Administration:** Please refer to SmPC for full information. Reconstitute with sterile unpreserved normal saline (0.9% sodium chloride for injection). **Blepharospasm:** Inject using a 27-30 gauge needle. The initial recommended dose is 1.25-2.5 U injected into the medial and lateral orbicularis oculi of the upper lid and the lateral orbicularis oculi of the lower lid. The initial dose should not exceed 25 U per eye but this can be subsequently increased. The total dose should not exceed 100 U every 12 weeks. **Spasmodic torticollis:** Inject using a 25-30 gauge needle in superficial muscles or 22 gauge into deeper musculature. Xeomin® is usually injected into the sternocleidomastoid, levator scapulae, scalenus, splenius capitis and/or the trapezius muscle(s). However the dosing should be tailored to the individual patient based on the head and neck position, location of pain, muscle hypertrophy, body weight and response. The maximum total dose is usually not more than 200 U but doses up to 300 U may be given. No more than 50 U should be given at any one injection site.

**Contra-indications:** Known hypersensitivity to Botulinum neurotoxin type A or to any of the excipients, generalised disorders of muscle activity (e.g. myasthenia gravis, Lambert-Eaton syndrome) and presence of infection at the proposed injection site. **Warnings and Precautions:** Adrenaline and other medical aids for treating anaphylaxis should be available. Xeomin® contains albumin a derivative of human blood. Prior to administration the physician must make himself familiar with the patient's anatomy and any changes due to surgical procedures. Side effects related to spread of botulinum toxin have resulted in death which in some cases was associated with dysphagia, pneumonia and/or significant debility. Patients with a history of dysphagia and aspiration should be treated with extreme caution. Patients or caregivers should be advised to seek immediate medical care

if swallowing, speech or respiratory disorders arise. Xeomin® should be used with caution if bleeding disorders occur, in patients receiving anticoagulant therapy, patients suffering from amyotrophic lateral sclerosis or other diseases which result in peripheral neuromuscular dysfunction and in targeted muscles which display pronounced weakness or atrophy. Reduced blinking following injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defects and corneal ulceration. Careful testing of corneal sensation should be performed in patients with previous eye operations. **Undesirable effects:** The following adverse reactions were reported with Xeomin®: Frequency by indication defined as: Common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100). **Blepharospasm:** Common: ptosis, dry eyes. Uncommon: paraesthesia, headache, conjunctivitis, dry mouth, skin rash, muscle weakness inflicted injury. **Spasmodic torticollis:** Common: dysphagia, muscle weakness, back pain. Uncommon: headache, tremor, eye pain, dysphonia, diarrhoea, dry mouth, vomiting, colitis, skin rash, erythema, pruritus, increased sweating, skeletal pain, myalgia, asthenia, injection site inflammation, injection site tenderness. **Xeomin® may only be used by physicians with suitable qualifications and proven experience in the application of Botulinum toxin. Prescriber should consult the SmPC for full information regarding side effects.**

**Legal Category:** POM. **Basic NHS Price:** 100 U/vial £119.90. Product Licence Number: PL29978/0001. **Marketing Authorisation Holder:** Merz Pharmaceuticals GmbH, 60048 Frankfurt Main, Germany. Further information available from: Merz Pharma UK Ltd., 260 Centennial Park, Elstree Hill South, Elstree, Hertfordshire WD6 3SR. Date of revision of text: January 2008. Xeomin® is a registered trademark of Merz GmbH. 1084/XEO/OCT/2008/JL

Adverse events should be reported. Reporting forms and information can be found at [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk). Adverse events should also be reported to Merz Pharma UK Ltd. at the address above, by e-mail to [UKdrugssafety@merz.com](mailto:UKdrugssafety@merz.com) or on 0845 009 0110.

Table 1: Mean change from baseline in BSDI scores three weeks after injection<sup>2</sup>

	Botox®		XEOMIN®	
	Number of patients	BSDI Score	Number of patients	BSDI Score
Male	35	-0.84	29	-0.81
Female	90	-0.82	100	-0.83
≤ 65 years	73	-0.79	63	-0.67
> 65 years	52	-0.86	66	-0.97

Table 2: Summary of adverse events reported with XEOMIN® (NT 201) and Botox® (BTXCo) in a pooled analysis of all studies.<sup>4</sup>

	NT 201 (n = 539)	BTXCo (n = 442)	Placebo (n = 75)
<b>Subjects with AEs (%):</b>			
	144 (26.7)	115 (26.0)	17 (22.7)
<b>Subjects with AEs (%) of intensity:</b>			
Mild	98 (18.2)	81 (18.3)	13 (17.3)
Moderate	63 (11.7)	43 (9.7)	5 (6.7)
Severe	9 (1.7)	5 (1.1)	2 (2.7)
<b>Subjects with SAEs (%):</b>			
	13 (2.4)	12 (2.7)	1 (1.3)
<b>Subjects with AEs (%) leading to:</b>			
Withdrawal:	2 (0.4)	1 (0.2)	0 (0.0)
Death:	0 (0.0)	1 (0.2)	1 (1.3)
Values are n (%) AE: Adverse events; SAE: Serious adverse events			

In a further poster, Professor Roggenkämper et al from the University Eye Clinic in Bonn, Germany presented a sub-analysis of his original paper<sup>7</sup> comparing outcomes of blepharospasm patients switched from Botox® to Xeomin®.<sup>3</sup>

In this prospective, multicentre, randomised, double-blind, active-comparator study, 300 patients with blepharospasm were randomised to receive either Xeomin® or Botox® at a maximum respective dose of 50 units per eye.

Within the study protocol, patients with a stable therapeutic response to Botox® were randomised to either maintain their existing Botox® dose or be switched to a matched dose of Xeomin®. As previously stated due to the differences in LD<sub>50</sub> assays used by different manufactures, unit doses are specific to individual products and are not interchangeable. In this study, a conversion factor of 1:1 was used, such that if a patient was stable on 25 (Allergan) units of Botox® they were switched to 25 (Merz) units of Xeomin®.

The poster reviewed a sub-analysis of outcomes by patient gender and age (≤65 years and >65 years) using explorative statistics to confirm the previous findings of comparative efficacy between Xeomin® and Botox® in patients with blepharospasm.

The mean changes in the Blepharospasm Disability Index (BSDI) baseline scores were measured three weeks after injection. Patients that switched from an established dose of Botox® to a matched dose of

Xeomin® were comparable between the groups with no relevant differences between the groups for age and gender being observed (Table 1).<sup>3</sup>

### Clinical safety of Xeomin®: a meta-analysis

Xeomin® is indicated for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults. Data presented in a poster by Dr Benecke from the Neurology Clinic in Rostock, Germany, presented the results of a meta-analysis of safety data from six controlled clinical trials (in patients with blepharospasm, cervical dystonia, post-stroke upper limb spasticity and healthy volunteers) involving 539 Xeomin®-treated subjects, 442 Botox®-treated subjects and 75 placebo-treated subjects.<sup>4</sup>

The meta-analysis demonstrated that (Table 2):<sup>4</sup>

- The incidence, type, and severity of adverse events (AEs) were similar in the Xeomin®-treated patients and the Botox®-treated patients.
- The incidence of serious AEs was low across all studies and all treatment groups.
- Most AEs reported with either Xeomin® or Botox® were mild or moderate in severity.
- The most common AEs (with an incidence ≥1%) in patients with cervical dystonia were dysphagia (a well-known injection site reaction), back and skeletal pain, and muscle weakness. The most common AEs in patients with blepharospasm were ptosis (another well-known injection site reaction), abnormal vision and back pain.
- Clinical laboratory evaluations showed no clinically-relevant safety signals.

The poster also included an analysis of the post-marketing surveillance from an estimated 62,000 patients treated with Xeomin® in clinical practice worldwide since the launch of Xeomin® in 2005.<sup>4</sup> The authors reported that no new safety concerns had been identified, and that the spontaneous reports identified from the surveillance either related to already well known safety concerns and/or were considered unlikely to be related to Xeomin® by the treating physician. The authors concluded that Xeomin® has a positive risk:benefit ratio, with a tolerability and safety profile comparable to Botox®.<sup>4</sup>

### Complexing proteins and BTX-A preparations: therapeutic benefit?

The role and clinical significance of complexing proteins in first-generation neurotoxin products has been the subject of ongoing debate, with some researchers suggesting that they may be required for product stability, to prolong neurotoxin persistence, and inhibit neurotoxin diffusion into adjacent tissues.<sup>8</sup> Others point out that complexing proteins have no proven therapeutic benefits, and may actually play a role in the formation of antibodies that neutralise botulinum neurotoxin,<sup>6,9</sup> thereby potentially leading to clinical failure.<sup>6</sup>

In a poster at Dystonia Europe 2008, by Eisele et al, an analysis of the dissociation of the 900kDa neurotoxin complex at various pH values was presented. The researchers found that the 900kDa neurotoxin complex, which was stable at a pH of 6, rapidly separated into several fractions when the pH increased towards one of physiological value, releasing the 150kDa neurotoxin from the protein complex with a half-life of less than one minute.<sup>5</sup>

The authors compared the efficient release of the 150kDa neurotoxin following injection in physiological conditions with the extended time to onset of therapeutic effect, which is typically measured in days.<sup>10</sup> The authors conceded that complexing proteins may be required to stabilise first generation neurotoxin formulations. However, they argued that based on these data, the concept that complexing proteins may stabilise the neurotoxin once injected into the muscle<sup>8</sup> or inhibit its diffusion<sup>11</sup> must now be questioned.

The authors concluded that the rapid release of the 150kDa neurotoxin from the 900kDa complex under physiological conditions aids in the understanding of comparable clinical efficacy and safety demonstrated between Xeomin® and a botulinum complex containing complexing proteins.<sup>5</sup>

### Product stability analysis

Unlike first generation neurotoxin complexes which require an effective cold-chain for storage and distribution, Xeomin® does not need to be refrigerated. An unopened vial can be safely transported and stored at room temperature conditions, of up to 25°C, for up to 3 years.<sup>1</sup> To validate these storage conditions Grein et al<sup>12</sup> performed a series of tests as defined in the ICH Q1A(R2) guideline on stability testing of drug products. Samples were stored at a range of temperatures including 5°C and 25°C and underwent a series of temperatures stress tests. Samples were tested in real time and under accelerated conditions using qualified incubators with narrow temperature tolerances.

The authors confirmed that there were no detrimental effects on the quality of Xeomin® across a range of temperature stress tests and that storage of Xeomin® at ambient conditions (25°C) for up to three years will not negatively affect its activity. The authors concluded that, in the case of Xeomin®, complexing proteins are not required to achieve product stability.<sup>12</sup>

#### KEY POINTS SUMMARY

Studies presented at Dystonia Europe 2008 (17–19 October 2008, Hamburg, Germany) have confirmed that:<sup>2,3,4,5,12</sup>

- Xeomin® is an effective treatment for the symptoms of spasmodic torticollis and blepharospasm
- Patients switched from their existing Botulinum toxin therapy to Xeomin® experienced comparable efficacy and tolerability
- Post-marketing surveillance of an estimated 62,000 patients worldwide has not identified any new safety concerns for Xeomin®
- Prior to reconstitution Xeomin® can be stored without refrigeration (≤25°) for up to three years

#### References

1. Xeomin® Summary of Product Characteristics. February 2008.
2. Jost WH, Grafe S, Comes G. *Efficacy of NT 201 in focal dystonia*. Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P31)
3. Roggenkämper P, Grafe S, Comes G. *Comparable outcomes of Xeomin® and Botox® in a prospective, randomized, double-blind, multicentre trial in patients suffering from blepharospasm*. Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P34)
4. Benecke R, Grafe S, Sassini I, Comes G. *Clinical safety of NT 201 (Xeomin®): a meta-analysis*. Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P33)
5. Eisele K-H, Taylor HV. *Dissociation of the 900 kDa neurotoxin complex for C. Botulinum under physiological conditions*. Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P09)
6. Benecke R, Jost WH, Kanovsky P et al. *A new botulinum toxin type A free of complexing proteins for treatment of cervical dystonia*. *Neurology* 2005;64:1949–51.
7. Roggenkämper P, Jost WH, Bihari K et al. *Efficacy and safety of a new Botulinum Toxin Type A free of complexing proteins in the treatment of blepharospasm*. *J Neural Transm* 2006;113:303–12.
8. Chen F, Kuziemko GM, Stevens RC. *Biophysical characterization of the stability of the 150-kilodalton botulinum toxin, the nontoxic component, and the 900-kilodalton botulinum toxin complex species*. *Infect Immun* 1998;66:2420–5.
9. Jankovic J, Vuong KD, Ahsan J. *Comparison of efficacy and immunogenicity of original versus current botulinum toxin in cervical dystonia*. *Neurology* 2003;60:1186–8.
10. Brin MF. *Dosing, administration, and a treatment algorithm for use of botulinum toxin A for adult-onset spasticity*. Spasticity Study Group. *Muscle Nerve* 1997;6:s208–20.
11. Carruthers A, Carruthers J. *Toxins 99, new information about the botulinum neurotoxins*. *Dermatol Surg* 2000;26:174–6.
12. Grein S, Mander GJ, Taylor HV. *NT 201 is stable without refrigeration: Complexing proteins are not required for stability of botulinum neurotoxin type A preparations*. Poster presentation at Dystonia Europe 2008, Hamburg, Germany, 17–19 October 2008. (P32)

Xeomin® prescribing information can be found on page 39.

#### EDITOR'S CHOICE

### Side-effects of anticonvulsants

In this study the authors take a fairly rigorous view of the studies they are assessing and in the tradition of meta-analyses many less rigorous studies are excluded. They identified adverse effects which occurred more frequently (+) or significantly more frequently (++) in the treatment arm than in the placebo arm. I have added weight change and my impression of some older drugs in purple. The study supports the view that most drugs have a similar range of toxic effects but that lamotrigine is cleaner than the others with regard to cognitive effects. Sodium channel blocking drugs all seem to cause ataxia and diplopia – as is commonly recognised in clinical practice. Topiramate only caused a trend towards depression; it is more of a problem in my clinical experience. This is representative of the problem with this study, which is that the less common but severe side effects such as major depression and psychosis are not common enough to reach clinical significance in the studies used, so that the differences between drugs are under-emphasised. It is nevertheless interesting to see that the similarities are greater than the differences; perhaps we should just toss a coin. – *MRAM*

*Zaccara G, Gangemi PF and Cincotta M.*

**Central nervous system adverse effects of new anti-epileptic drugs. A meta-analysis of placebo- controlled studies.**

**SEIZURE**

**2008;17:405-21.**

	CBZ	GBP	LAM	LEV	OXC	PGB	SVA	TOP	ZON
Somnolence	++	++	+	++	++	++	++	++	++
Fatigue	++	+	+	++	++	++	++	++	+
Dizziness	++	++	++	+	++	++	+	++	++
Ataxia/diplopia	++	+	++	+	++				
Tremor		+	+	++			++		
Cognitive	+					+	+	++	
Anxiety								+	
Depression				+				+++	+
Psychosis				+					
Psychological behavioural				+				+	+
Headache		+	++	+	+	+	+	+	+
Weight change	++					++	++	-	

†/++ Mx subjective view

### DEPRESSION: prevention of perinatal depression

If you identify depression in the last trimester of pregnancy, is there anything you can do to promote remission.. and avoid all the harmful consequences of poor bonding with the child? Well, intervention X reduces the prevalence of depression at 6 months after birth from 53% to 23%, and this effect is sustained for 12 months. Not bad. But what is remarkable is that agent X is not a drug, but cognitive behavioral therapy; more surprising still it is administered not to the affluent eloquent but to unselected mothers in rural Pakistan. People charmingly referred to as “Lady Health Workers” had a brief training and then administered one session of CBT every week for 4 weeks in the last month of pregnancy, three sessions in the first postnatal month, and nine 1-monthly sessions thereafter. The cost of this is not laid out. Sadly for the investigators, none of the infant-related outcomes differed significantly. Good on the Wellcome for funding work on an unglamorous condition, with negative pharmaceutical value, amongst overlooked peoples. – *AJC*

*Rahman A, Malik A, Sikander S, Roberts C, Creed F.*

**Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial.**

**LANCET**

**2008;372(9642):868-9.**

### HEADACHE: transformed migraine and analgesia

#### ★★★ RECOMMENDED

Two point five percent of those with episodic migraine converted to chronic (transformed) migraine over a one year period. This report, which won the Harold G Wolff Lecture award for 2008, comes from the massive 120,000 population study (the American Migraine Prevalence and Prevention Study),