Botulinum toxin type A (Xeomin)

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Summary

- Xeomin is a pure botulinum toxin type A (BTX-A) preparation licensed for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults.
- The lack of protein complexes in the Xeomin preparation is suggested to be associated with a reduced risk of immunogenicity and reduced number of secondary non-responders.
- Xeomin is the fourth BTX-A preparation to be licensed in the UK.
- The botulinum toxin units used in each preparation are specific to that product and are not interchangeable.
- Xeomin is the only BTX-A preparation that can be stored at room temperature, which reduces the risk of product wastage and removes the need for cold chain storage and distribution between pharmacy and clinics.
- Two phase III studies have compared Xeomin to Botox, for the treatment of blepharospasm and spasmodic torticollis.
- What these two studies show is that a single dose of Xeomin is as effective as a single dose of Botox in treating blepharospasm and spasmodic torticollis, in patients who have already shown response to Botox: no treatment-naïve patients were enrolled.
- In both of these studies a single dose of BTX-A was administered. This provides no evidence of non-response or development of immunogenicity. Long-term clinical studies with antibody testing are required to confirm these claims.
- Xeomin has been compared with placebo in a single dose efficacy and safety study in patients with upper-limb spasticity post-stroke. Xeomin is not yet licensed for this indication. Xeomin treatment was more effective than placebo in reducing muscle tone in the flexors of the wrist, forearm, elbow and thumb, and improvement functional ability.
Background

Xeomin was launched in January 2008 for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational form (spasmodic torticollis) in adults. Both of these conditions are torsion dystonias; a dystonia is a movement caused by prolonged muscular contraction. Dystonic spasms can develop around the neck, usually in the third to fifth decade. These can cause the head to turn (torticollis), be drawn backwards (retrocollis) or forwards (antercollis). Blepharospasm is a progressive, spasmodic, bilateral, intermittent or persistent involuntary contraction of the orbicular oculi muscles, thought to be caused by abnormal functioning of the basal ganglia. Spasmodic and repetitive eye contractions can lead to functional blindness in up to 15% of patients. Botulinum toxin, when carefully sited by injection, can help with both of these dystonias, albeit on a temporary basis.

Botulinum neurotoxin A blocks cholinergic transmission at the neuromuscular junction by inhibiting acetylcholine release. The nerve terminals at the neuromuscular junction will no longer respond to nerve impulses and secretion of acetylcholine is prevented. The formation of new nerve terminals and motor endplates establishes recovery of impulse transmission. Recovery after intramuscular injection takes place normally within 12 weeks of injection as nerve terminals sprout and reconnect with the endplates.

Xeomin (NT201) has been developed as a formulation of pure BTX-A, free of complexing proteins, which are present in other BTX-A preparations. These complexing proteins may play a role in the formation of antibodies that neutralise BTX-A. The issue of immunogenicity is of concern as dystonias are chronic conditions that require long term therapy. Xeomin has not been associated with any biologically relevant immunogenicity in animal models, unlike the BTX-A complex, and there is likely to be associated with fewer neutralising antibodies and reduced numbers of secondary non-responders. The proportion of secondary non-responders can be as high as 10% and 40% of patients can develop titres of non-neutralising antibodies.

Xeomin is the fourth botulimum toxin A (BTX-A) preparation to be launched in the UK; the others are Botox, Dysport and Vistabel. The botulinum toxin units used in each preparation are specific to that product and are not interchangeable. The licensed indications for the preparations are detailed in table 1. Xeomin is the only BTX-A preparation that can be stored at room temperature, which reduces the risk of product wastage and removes the need for cold chain storage and distribution between pharmacy and clinics.

The Scottish Medicines Consortium has approved the use Xeomin within NHS Scotland for the symptomatic management of blepharospasm and cervical dystonia of a predominantly rotational kind (spasmodic torticollis) in adults.

Clinical studies: licensed indications

Two phase III studies using Xeomin have been carried out, one for blepharospasm and one for spasmodic torticollis (cervical dystonia). In both studies, patients had received previous doses of Botox; no study used patients who were treatment-naïve, as may be seen in actual clinical practice. Previous studies had shown that identical units of Xeomin and Botox were equally effective, so the doses used in both studies were based on two pre-study Botox injections each patient had received.
Blepharospasm

The efficacy and safety of Xeomin was compared with Botox in 304 patients with blepharospasm in a non-inferiority, randomised, blinded study. Patients were required to have had at least two previous BTX-A injections resulting in a stable therapeutic response. The majority of patients were female (72.7%), which reflects the higher prevalence of the condition in women. The intention-to-treat (ITT) population comprised of 148 patients receiving Xeomin and 152 receiving Botox; of these 19 and 25 respectively were excluded from the per protocol (PP) population (n=256).

The mean total doses of study medication were 39.6±13.3 units of Xeomin and 40.8±14.2 units of Botox.

The primary efficacy variable was the change from baseline in the Jankovic Rating Scale (JRS) at the control visit, which was three weeks after the baseline visit. The JRS scale ranges from 0 to 8, with two categories, severity and frequency of symptoms. The adjusted mean JRS score at the control visit was -2.90 for the Xeomin group and -2.67 for the Botox group. These changes were significant (p<0.0001), demonstrating that both were effective in improving the symptoms of blepharospasm. The difference of -0.23
had an upper 95% CI of 0.22; this was below the predefined limit for non-inferiority (0.8), demonstrating that Xeomin was non-inferior to Botox. There was no statistically significant difference between the groups (p=0.31).

Secondary efficacy variables included the changes from baseline in the sum score of the JRS at the final visit (between days 109-112) and in the mean total score of the Blepharospasm Disability Index (BSDI) at the control and final visits. The BSDI assesses daily activities such as reading, driving, watching television, shopping and walking, on a scale of 0 (no impairment) to 4 (not possible due to disease). Patients also evaluated the global response to the study treatment at both visits. There were no statistically significant differences between the two treatment groups for the secondary variables, which supports the non-inferiority of Xeomin vs. Botox. In both groups, both the JRS sum scores at the final visit and the BSDI scores at the control and final visits were significantly reduced from baselines, (p<0.0001 for all), indicating an improvement in daily functioning. Patients in both treatment groups reported marked improvement of their symptoms. Slightly more investigators rated the efficacy of Xeomin as 'very good' (34.9%) than Botox (28.4%), but this difference was not statistically significant. There was no difference in the median duration of effect (110 days), time to onset of effect (4 days) and waning of treatment effect (11 weeks) between the treatment groups.

Both Xeomin and Botox were well tolerated and no patient discontinued the study early because of adverse events (AEs). No statistically significant differences in the incidences of side effects were observed between the treatment groups. Over 90% of the AEs were graded mild or moderate. The most common event was ptosis, occurring in 6.1% of patients having Xeomin and 4.5% having Botox. All cases were judged to be treatment-related. Abnormal vision was more common in the Botox group (3.2% vs. 1.35%), though only three of the five cases in the Botox group were thought to be treated related. Xerophthalmia (dry eyes), related to Xeomin treatment only, occurred in 2% of patients. Serious adverse events were not considered related to treatment.

Table 2: Pharmaceutical properties of botulinum toxin A preparations

<table>
<thead>
<tr>
<th>Excipients</th>
<th>Shelf life of unopened vial</th>
<th>Reconstitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeomin¹ 100 units per vial</td>
<td>Human albumin and sucrose</td>
<td>3 years at temperatures up to 25°C. Reconstitute with 0.9% sodium chloride to give a range of concentrations from 1.25 units/0.1ml to 20 units/1.0ml. Reconstituted product should be use immediately but can be stored for 24 hours at 2-8°C.</td>
</tr>
<tr>
<td>Botox² 100 units per vial.</td>
<td>Human albumin, sodium chloride</td>
<td>3 years. Store in a refrigerator (2-8°C) or freezer (below -5°C). Reconstitute with 0.9% sodium chloride to give a range of concentrations from 1.25 units/0.1ml to 20 units/0.1ml. Reconstituted product should be use immediately but can be stored for 24 hours at 2-8°C.</td>
</tr>
<tr>
<td>Dysport³ 500 units per vial.</td>
<td>Human albumin, lactose.</td>
<td>24 months at 2-8°C. Reconstitute with 0.9% sodium chloride to give 500 units/ml, except for blepharospasm, when 2.5mls is used to give a 200 units/ml solution. Reconstituted product should be use immediately but can be stored for 8 hours at 2-8°C.</td>
</tr>
<tr>
<td>Vistabel⁵ 50 and 100 units per vial.</td>
<td>Human albumin, sodium chloride.</td>
<td>24 months at 2-8°C. Reconstituted solution of 4 units per 0.1ml. Reconstituted product should be use immediately but can be stored for 4 hours at 2-8°C.</td>
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</tbody>
</table>
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**Spasmodic torticollis (cervical dystonia)**

In this randomised, double-blind, non-inferiority study 466 patients with spasmodic torticollis were randomised to receive a single dose of either Xeomin or Botox. Patients were monitored for 112 days (16 weeks). The ITT population was 463, 231 having Xeomin and 232 on Botox and the PP population was 420 (213 and 207 respectively). The primary efficacy variable was the change from baseline in the Toronto Western Spasmodic Torticollis Scale (TWSTRS) severity score at the control visit (28±7 days post injection, range 0-35). The secondary efficacy variables included the TWSTRS severity score at final visit, the TWSTRS pain subscore (range 0-5), the Visual Analogue Scale (VAS) Pain (100mm) score, responder rates (improvements in >20% in the TWSTRS severity score at the control visit and the investigators assessment of efficacy at the final visit.

The total amount of study medication used for all muscles treated in one injection session was 140.4±51.4 units of Xeomin and 138.9±46.8 of Botox. The median TWSTRS severity score fell from a median of 18 at baseline to 11 at the control visit (p<0.0001 for both groups), indicating an improvement in symptoms. The difference of -0.33 points between the treatment groups was lower than the predefined inferiority margin of 1.3, indicating non-inferiority of Xeomin vs. Botox. No significant difference was seen between treatment groups for any of the secondary variables, all of which indicated an improvement in symptoms. The difference in -0.33 points between the treatment groups was lower than the predefined inferiority margin of 1.3, indicating non-inferiority of Xeomin vs. Botox. No significant difference was seen between treatment groups for any of the secondary variables, all of which indicated an improvement in symptoms compared with baseline. There was no difference in the median duration of effect (~95 days), time to onset of effect (~7 days) and waning of treatment effect (~10 weeks) between the treatment groups.

The most frequently reported adverse event was dysphagia, which occurred in 10.8% of the Xeomin and 8.2% of the Botox groups. No significant differences in the incidences of adverse events were seen between the treatment groups.

What these two studies show is that a single dose of Xeomin is as effective as a single dose of Botox in treating blepharospasm and spasmodic torticollis, in patients who have already shown response to Botox. As already mentioned the lack of protein complexes in the Xeomin preparation is suggested to be associated with a reduced risk of immunogenicity and reduced number of secondary non-responders. In both of these studies a single dose of BTX-A was administered. This provides no evidence of non-response or development of immunogenicity. Long-term clinical studies with antibody testing are required to confirm these claims.

**Clinical studies: unlicensed indications**

The efficacy and safety of Xeomin in the treatment of 148 patients suffering from upper limb post-stroke spasticity of the wrist and fingers, has been presented in both abstract and poster format. Patients were randomised to either Xeomin (n=73) or placebo (n=75) and were followed up to 20 weeks after the dose. Wrist and finger muscles were treated; other muscles were treated as necessary. The doses were those recommended by the WE MOVE Spasticity Study Group and up to 435 units were administered (mean: 307 units).

The primary outcome was responder rate at week 4. Responders were defined as those with at least a 1-point reduction in the Ashworth score for wrist flexors from baseline. Responder rates at week 4 were significantly higher in the Xeomin group compared with the placebo group, as would be expected: wrist flexors 68.5% vs. 37.3%, finger flexors 68.5% vs. 36.0%, elbow flexors 63.0% vs. 38.2%, forearm pronators 54.3% vs. 31.6% and thumb flexors 65.4% vs. 35.5%. This shows that Xeomin was more effective in reducing muscle tone than placebo. The Odds Ratios ranged from 3.12 to 13.43, p≤0.009 for all treated flexor muscle groups. These statistically significant improvements were seen at all post-injection site visits until week 12 only, though patients treated with Xeomin were more likely to be responders up to the final visit, compared with those treated with placebo.
Efficacy of treatment was rated as good or very good in more patients treated with Xeomin than placebo, (56.2% vs. 28.0% and 9.6% vs. 2.7% respectively, p≤0.001), as rated by the investigators, carers and patients. More patients treated with placebo than Xeomin rated the treatment as poor (44.0% vs. 20.5%). Xeomin was statistically significantly superior in all domains evaluated by the Disability Assessment scale: improvements in 'hygiene' and 'limb position' were seen up to week 8 (p≤0.05 and p≤0.09 respectively); 'pain' up to week 4 was more bearable with Xeomin treatment (p≤0.042) and 'dressing' was significantly easier with Xeomin treatment at week 2 (p=0.003)\(^1\).

The data from this trial is not yet fully published. As would be expected, Xeomin was more effective than placebo after a single dose for treating upper limb spasticity post-stroke. The authors do not say why this was a single dose trial, as multi-dose study would be useful, considering that data on repeated and long-term treatment are limited.\(^4\) The peak effects of Botox when used for focal spasticity associated with stroke are generally seen 4-6 weeks following treatment, as seen in this trial.

Xeomin is not yet licensed for the treatment of patients suffering with upper-limb post-stroke spasticity.\(^1\)

Reference List


(8) Summary of Product Characteristics. Dysport. Ipsen Ltd. Accessed via [http://emc.medicines.org.uk](http://emc.medicines.org.uk), on 05/12/08. Date of revision of
the text: June 2007.


