Profile of Xeomin® (incobotulinumtoxinA) for the treatment of blepharospasm

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Abstract: Even though conventional botulinum neurotoxin (BoNT) products have shown successful treatment results in patients with benign blepharospasm (BEB), the main, potential long-term side effect of BoNT use is the development of immunologic resistance due to the production of neutralizing antibody to the neurotoxin after repeated injections. Xeomin® (incobotulinumtoxinA), a unique botulinum neurotoxin type A (BoNT/A) drug free of complexing proteins otherwise contained in all conventional BoNT/A drugs, was recently approved by US Food and Drug Administration for the treatment of cervical dystonia or blepharospasm in adults. The newly approved BoNT/A drug may overcome this limitation of previous conventional products, since it contains pure neurotoxin (150 kDa) through a manufacturing process that separates it from complexing proteins such as hemagglutinins produced by fermentation of Clostridium botulinum. Many studies have also shown that Xeomin® has the same efficacy and safety profile as complexing protein-containing products such as Botox® and is exchangeable with Botox® using a simple 1:1 conversion ratio. Xeomin® represents a new treatment option for the repeated treatment of patients with blepharospasm in that it may reduce antibody-induced therapy failure. But, long-term comparative trials in naïve patients between Xeomin® and conventional BoNT/A drugs are required to confirm the low immunogenicity of Xeomin®.

Keywords: blepharospasm, botulinum neurotoxin type A, Xeomin®, incobotulinumtoxinA, complexing proteins, neutralizing antibodies

Introduction

Blepharospasm is a localized form of dystonia consisting of involuntary tonic and spasmodic contractions of the orbicularis oculi, corrugator supercilii, and procerus muscles, leading to partial or complete closure of the eyelids. These contractions may be intense and last from several seconds to a few minutes.1

It is a bilateral condition with tonic rather than clonic spasms, which develops typically between 50 and 70 years of age. Women appear to be more affected than men. The exact cause remains unknown, but may result from damage to areas of the basal ganglia including the superior colliculus, pars reticularis of the substantia nigra, and nucleus raphe magnus. The most common form is called benign essential blepharospasm (BEB), which is limited to the orbitopalpebral area.1 Botulinum toxin (BoNT) injections were first used to treat strabismus in 1977 by Alan Scott, a pediatric ophthalmologist,2 and subsequently used to treat blepharospasm in the early 1980s by Frueh et al3 and Scott et al.4 BoNT is highly effective and well tolerated in the symptomatic treatment of a very broad range of conditions involving either muscle hyperactivity such as blepharospasm or cervical dystonia, or cholinergic hyperactivity.
such as hyperhidrosis or hypersalivation.5,6 Recently, BoNT has been approved for the treatment of glabellar rhytids and migraine headaches.7

BoNTs act on the peripheral nervous system where they inhibit acetylcholine exocytosis at the motor endplate within the neuromuscular junction by inhibition of proteolytic cleavage of different proteins of the acetylcholine transport protein cascade (soluble N-ethylmaleimide-sensitive fusion attachment protein receptor (SNARE) proteins). Botulinum toxin type A (BoNT/A) hydrolyses SNAP-25 (synaptosomal-associated protein 25) which is located on the presynaptic cell membrane whereas type B (BoNT/B) acts on synaptobrevin or VAMP (vesicle-associated membrane protein) which is embedded in the acetylcholine vesicle membrane. By cleaving these target proteins, BoNT prevents the fusion of the synaptic vesicle with the presynaptic membrane, thereby blocking the release of acetylcholine in the synaptic cleft. Between a heavy chain (100 kDa) and a light chain (50 kDa) of neurotoxin, only the light chain is responsible for the pharmacological action of BoNT.1,8

The various strains of the anaerobic bacterium Clostridium botulinum produce 7 distinct serotypes of botulinum toxin, of which 5 are pharmacologically active in man (A, B, E, F, and G) and 2 are inactive (C and D).9 Today, 2 serotypes are used in therapeutics, botulinum toxin type A and type B.

In August, 2010 the US Food and Drug Administration (FDA) approved Xeomin® (incobotulinumtoxinA; Merz Pharmaceuticals GmbH, Frankfurt, Germany) for the treatment of cervical dystonia or blepharospasm in adults (Figure 1). Now Xeomin® is the fourth BoNT product licensed for the US market, following Botox® (onabotulinumtoxinA; Allergan Inc, Irvine, CA), Dysport® (abobotulinumtoxinA; Ipsen Ltd, Slough, Berks, UK), and Myobloc® (rimabotulinumtoxinB; Solstice Neurosciences Inc, Malvern, PA).11 With this recent entry, 3 type A and 1 type B brands of botulinum neurotoxins are available in the US9 (Table 1).

The main long-term side effect of BoNT use is the development of an immunologic resistance due to the production of neutralizing antibody for the neurotoxin after repeated injections. The frequency of this sensitization reported by several authors is around 3% to 10%.12 The newly approved BoNT/A drug may overcome this limitation of the other 3 previous products, since Xeomin® contains only the pure neurotoxin (150 kDa) through a manufacturing process that separates it from complexing proteins such as hemagglutinins (HA) and other proteins in the neurotoxin complex produced by fermentation of C. botulinum.11

**Xeomin®; BoNT/A preparation free of complexing proteins**

Xeomin® was first introduced in Germany in July, 2005.13,14 It received approval for the treatment of blepharospasm and cervical dystonia in a number of European countries, and then Argentina and Canada, for the treatment of blepharospasm, cervical dystonia, and poststroke upper-limb spasticity,15 and now in the US for cervical dystonia and blepharospasm. The FDA’s approval of Xeomin® for the treatment of blepharospasm restricts the drug to adult patients previously treated with Botox®. Therapy with the newer BoNT/A product should be based on the previous dose, number, and location of Botox® injections. Regardless of whether the patient has cervical dystonia or blepharospasm, the treatment sessions should occur no more frequently than every 12 weeks. Xeomin® is supplied in single-use vials containing 50 or 100 units of lyophilized incobotulinumtoxinA, which do not require refrigeration before use.11

In all naturally occurring serotypes of botulinum toxin (types A–G), the active neurotoxin (150 kDa; 100 kDa of a heavy chain and 50 kDa of a light chain) is noncovalently associated with a set of nontoxic and inactive complexing proteins (hemagglutinins [HA] and non-hemagglutinins [NHA]) and thus forms high molecular toxin complexes.6,16–18 The molecular weight of the toxin complex ranges between 230 and 900 kDa, depending on the serotype.1 All previous BoNT drugs, including Botox® and Dysport®, contain these nontoxic and inactive complexing proteins in addition to the neurotoxin (Figure 2).6 This new preparation, Xeomin®, is derived from a wild-type strain of C. botulinum type A.

*Figure 1* Recently US FDA approved botulinum toxin type A, Xeomin® (incobotulinumtoxinA).
Xeomin® treatment in BEB (ATCC 3502) which is the same strain from which Botox® is derived and thus has similar biologic activity to Botox®.17,19 Unlike Botox®, it contains only the active neurotoxin moiety with complexing proteins removed through a manufacturing process for removal all clostridial contaminants.6,11

Clinical functions of complexing proteins
The function of the nontoxic portions of the protein complexes in BoNT/A preparations has been studied. It was initially thought that these proteins protected the native neurotoxin from destruction in the gastrointestinal tract with oral ingestion (its natural route of entry).18,20 This was subsequently confirmed in biochemical analyses (protease resistance) of different toxin serotypes.21 Others have suggested that complexing proteins may have a role in the uptake and transcytosis of botulinum toxin through the intestinal epithelium to reach and affect muscle.22–24 Xeomin® does not have complexing proteins to protect it from the low pH and gastric enzymes and therefore shows poor oral bioavailability and toxicity.25 However, in the therapeutic setting these proteins are not relevant to clinical efficacy.

Another consideration is that complexing proteins may in fact limit botulinum toxin diffusion from the injection site and thereby minimize adverse events, due to the large size of the toxin complex.26–28 The smaller size of Xeomin® might more rapidly and easily diffuse away from the target tissue into adjacent tissues and produce an adverse effect profile different from other BoNT/A drugs. However, an in vivo study using Botox®, Dysport®, and a purified preparation of BoNT/A (150 kDa) showed that diffusion from the injection site does not differ between the 3 preparations.29 Another study using 125I-radiolabeled botulinum toxin type A showed no difference in the diffusion of the free or complexed form of BoNT/A after injection into the muscle, even when using high doses.30 Comparing the adverse effect profiles of conventional BoNT/A drugs and complexing protein-free BoNT/A drug, indeed, did not reveal any of those differences.5,13,14,31,32 These findings can be explained by a dissociation of the complex consisting of neurotoxin and complexing proteins immediately after injection.33 At physiologic pH values, the active 150 kDa neurotoxin is efficiently released in less than 1 minute from the 900 kDa complex.34 This is in contrast with the onset time of its therapeutic effect, which is mea-

Table 1 Properties of different botulinum toxin preparations

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Botox®</th>
<th>Dysport®</th>
<th>Xeomin®</th>
<th>Myobloc®/Neurobloc®a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
<td>OnabotulinumtoxinA</td>
<td>AbobotulinumtoxinA</td>
<td>IncobotulinumtoxinA</td>
<td>RimabotulinumtoxinB</td>
</tr>
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<td>Manufacturer</td>
<td>Allergan Inc (USA)</td>
<td>Ipsen Ltd (UK)</td>
<td>Merz Pharmaceuticals GmbH (Germany)</td>
<td>Solstice Neurosciences Inc (USA)</td>
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<tr>
<td>Serotype</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Target SNARE</td>
<td>SNAP-25</td>
<td>SNAP-25</td>
<td>SNAP-25</td>
<td>VAMP (synaptobrevin)</td>
</tr>
<tr>
<td>Packaging (units/vial)</td>
<td>100</td>
<td>500</td>
<td>50, 100</td>
<td>2500 (0.5 mL), 5000 (1 mL), 10,000 (2 mL)</td>
</tr>
<tr>
<td>Pharmaceutical preparation</td>
<td>Powder</td>
<td>Powder</td>
<td>Powder</td>
<td>Ready-to-use solution (5000 U/mL)</td>
</tr>
<tr>
<td>Stabilization</td>
<td>Vacuum drying</td>
<td>Freeze drying</td>
<td>Vacuum drying</td>
<td>pH reduction</td>
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<tr>
<td>Complex size (kDa)</td>
<td>900</td>
<td>300–900</td>
<td>150</td>
<td>X</td>
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<tr>
<td>Complexing proteins</td>
<td>O</td>
<td>O</td>
<td>X</td>
<td>O</td>
</tr>
<tr>
<td>Excipients (per vial)</td>
<td>HSA 500 ug NaCl 900 ug</td>
<td>HSA 125 ug Lactose 2500 ug</td>
<td>100 units/vial</td>
<td>HSA 0.5 mg/mL disodium succinate 0.01 M</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NaCl 0.1 M</td>
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<td></td>
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<tr>
<td>Biological activity in relation to Botox®</td>
<td>1</td>
<td>1/3</td>
<td>1</td>
<td>1/40</td>
</tr>
<tr>
<td>Specific activity (units/ng)</td>
<td>20</td>
<td>40</td>
<td>167</td>
<td>75–125</td>
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<tr>
<td>Storage of packaged product</td>
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<td>2°C–8°C</td>
<td>Room temperature</td>
<td>2°C–8°C</td>
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<tr>
<td>Shelf life</td>
<td>36 months</td>
<td>24 months</td>
<td>36–48 months</td>
<td>24 months</td>
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<td>pH of reconstituted preparation</td>
<td>7.4</td>
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<td>7.4</td>
<td>5.6</td>
</tr>
<tr>
<td>Storage once reconstituted</td>
<td>2°C–8°C for 24 hours</td>
<td>2°C–8°C for several hours</td>
<td>2°C–8°C for 24 hours</td>
<td>For a few hours</td>
</tr>
</tbody>
</table>

Notes: *Myobloc® is the brand name in Canada, the United States, and Korea. Neurobloc® is the brand name in the European Union, Norway, and Iceland.
Abbreviations: HSA, human serum albumin; VAMP, vesicle associated membrane protein.
sured in days. Therefore, complexing proteins do not seem to be essential for either the stability of the 900 kDa toxin complex at physiologic pH or for limiting diffusion of the 150 kDa neurotoxin after injection of conventional BoNT/A preparation.19

Another possible function of complexing proteins in a therapeutic setting could be to enhance the stability of the botulinum toxin drug during storage before use. However, a series of stability studies (stress experiments) of Xeomin® do not support this hypothesis. The stability of Xeomin® was evaluated in both long-term storage studies and in short-term temperature-stress studies. The studies evaluated the active ingredient (neurotoxin) and inactive ingredients (sucrose and human serum albumin [HSA]) of vials containing Xeomin® stored at 5°C or 25°C, as well as the biologic activity of the neurotoxin (mouse median lethal dose [LD₅₀]). After 48 months of storage in a refrigerator (5°C) or at room temperature (25°C), no significant changes in neurotoxin, sucrose, or HSA content or, more importantly, biologic activity, were observed in the Xeomin®. Furthermore, storage studies showed that Xeomin® was stable for at least 18 months at 30°C and for at least 6 months at 40°C. Also in short-term temperature-stress studies, there was neither loss of activity nor degradation detectable after 30 days at 60°C. Even at 80°C, the reduction of biologic activity occurred within 5 days, although proteolytic activity had not fallen to below one-third of the initial value after 10 days, with a decline over time considerably slower than for biologic activity.35 Overall, these results demonstrate that complexing proteins are not required to maintain the stability of BoNT/A preparations during storage.19 The manufacturer reports that Xeomin® is stable at room temperature for 3 years and new data demonstrate stability for 4 years at room temperature.11,36

Complexing proteins may have the disadvantage of immunostimulation, since HA, which belong to the complexing proteins, are lectins known as potent stimulators of immune cells.11 Lee et al37 reported vaccination experiments in mice with formalin-treated botulinum toxin type B (toxoid). The amount of neutralizing antibodies increased when the neurotoxoid was complexed with HA, compared with the neurotoxoid complexed with NHA, or when the neurotoxoid was administered alone. Further analysis showed that among the 4 subcomponents of HA designated HA1, HA2, HA3a, and HA3b, HA1 and HA3b subcomponents of HA accounted for the adjuvant activity. The mechanism of increased immune response to HA1 and HA3b appeared to be mediated by an increase in interleukin-6, leading to increase in CD19+ cells. Further experiments showed that in vitro enzyme-linked immunosorbent assay analysis of antibody binding to BoNT/A large toxin complex showed that HA1 was responsible for most of the immunogenic response.37 Some have commented that this study was flawed and does not reflect a therapeutic situation. The dose of toxin used was about 1000 times greater than in typical clinical use. The antigen immunized into the mice was actually inactivated toxin (toxoid) that was treated with formaldehyde, which in itself causes the molecule to be more antigenic than native proteins.38 However, these and other data confirmed that HA1 and HA3b appear to increase the immunogenic potential.37

Hence the presence of complexing proteins in commercially available BoNT/A preparations may facilitate an immunogenic reaction and the development of neutralizing antibodies against the active neurotoxin leading to partial or complete clinical unresponsiveness (treatment failure) to BoNT/A.19 Indeed, incidence of antibody development following treatment with Botox® had been significantly reduced since its original formulation was changed to reduce complexing proteins and inactive neurotoxin.39,40 Furthermore, removing the complexing proteins in the manufacture of Xeomin® may reduce this risk markedly. Preliminary experiments with Xeomin® also suggest that the absence of complexing proteins is indeed associated with reduced immunogenicity. In a preclinical animal study with Cynomolgus monkeys, repeated injections with 4, 8, or 16 U/kg Xeomin® or control were not associated with the development of neutralizing antibodies in each group, despite clear evidence of biologic activity of the neurotoxin, particularly in the highest-dose group.41 The immunogenicity of Xeomin® was compared with that of Botox® and Dysport® in New Zealand white rabbits. After repeated injection, Xeomin® did not induce the formation of neutralizing antibodies, unlike the other preparations.42

Similar results were shown in a human study of up to 89 weeks in patients with upper limb spasticity who received
multiple injections of Xeomin®; no patient developed neutralizing antibodies throughout the study.33 Although in the clinical development program of Xeomin® in the US, 12 of 1080 subjects developed antibodies against the neurotoxin, each of these patients was previously treated with a conventional BoNT/A product which contained complexing proteins. They may have already been primed by the previous treatment.44

Several risk factors of this sensitization have been identified:12,45 injection of over 100 units of Botox® or 300 units of Dysport® per session, interval of less than 3 months between 2 injections, ‘Booster’ technique where another dose is injected 2 to 3 weeks after the first injection, and use of a BoNT drug with a low intrinsic activity. Cumulative dose, treatment time, and patient age have been excluded as risk factors. Antibody-induced therapy failure usually develops within the first 2 to 3 years of BoNT therapy.46

Among the above risk factors, the intrinsic activity of BoNT drugs is defined as the number of toxin units per the amount (nanogram) of clostridial proteins (ie, toxin complex). At each injection of toxin, the administered protein mass will be greater when using a toxin with a low intrinsic activity. The toxin’s antigenic potential is probably related to the total protein concentration injected (protein load), and according to Borodic et al,47 this may be a much more relevant parameter in the development of a resistance than the number of units. Indeed, in patients with cervical dystonia, the original formulation of Botox® (100 U/25 ng protein) was 6 times more likely to elicit the production of neutralizing antibodies than the newer formulation of Botox® (100 U/5 ng protein) which contains fewer complexing proteins and reduced inactive neurotoxin. The authors conclude that the low risk of antibody formation after newer Botox® treatment is related to lower protein load.39

Xeomin® contains only 0.6 ng of clostridial proteins per vial (100 U/0.6 ng protein), whereas the other products contain much more protein: 55 ng in Myobloc®, 5 ng in Botox® (100 U/5 ng protein), and 12.5 ng in Dysport® (500 U/12.5 ng protein).11

Based on a conversion factor of 1 Botox® or Xeomin® unit to 3 Dysport® units,6,48–50 100 units of Botox® or Xeomin® are bioequivalent to 300 units of Dysport®. If this same equivalent dose of the preparations is injected, in the case of Xeomin®, the patient is treated with 0.6 ng of clostridial protein (neurotoxin alone). In contrast, when treated with Botox® or Dysport®, the patient receives a much higher amount of clostridial proteins including complexing proteins, 5 ng or 7.5 ng respectively (Figure 3). In other words, Xeomin® contains the lowest amount of BoNT/A with respect to units. Thus it has the highest specific potency, and with Xeomin® the patients gets the lowest amount of foreign protein,11 so that the risk of development of any immunogenicity may be reduced.

But long-term, trials in naïve patients comparing Xeomin® with conventional BoNT/A drugs are required to confirm the low immunogenicity of Xeomin®.

**Efficacy and safety profile of Xeomin®**

Based on the fact that Xeomin® is obtained from the same strain of *C. botulinum* as Botox® and on preclinical studies, the manufacturer first assumed Xeomin® had the same potency as Botox®. Subsequently, the registration studies using a cross-over design were based on identical potency labeling. The result of equivalent experiments in which LD₅₀ of 5 different batches of Xeomin® and Botox® was compared in a blinded fashion demonstrates that there was no difference in the potency between the 2 preparations.51 Results from both registration studies13,14 together with subsequent head-to-head potency testing using a mouse lethality (LD₅₀) assay17 confirmed the equivalence rate between Xeomin® and Botox®. The conclusion of a focal dystonia study also showed that Xeomin® had the same efficacy as Botox®, which means that 1 unit of Xeomin® is equipotent to 1 unit of Botox®.6 Dressler50 further confirmed the identical potency labeling by his study converting Botox® in a blinded fashion to Xeomin® using a 1:1 conversion ratio. Therefore, clinically Xeomin®

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**Figure 3** Amount of clostridial protein (blue) of neurotoxin (red) applied in the treatment of benign essential blepharospasm (BEB). Dose 100 units of Xeomin® or Botox®, 300 units Dysport®.
and Botox® can be exchanged easily using a straightforward 1:1 conversion ratio.50

The efficacy and safety of Xeomin® in the treatment of blepharospasm has been confirmed by a prospective, double-blind, placebo-controlled, randomized, multicenter study.31,32 In this study involving 109 patients (mean total dose of Xeomin® per treatment visit was 64.8 units), the Jankovic Rating Scale (JRS) severity score was significantly reduced compared with placebo (P < 0.001). And the most commonly reported adverse effects related to Xeomin® vs placebo were eyelid ptosis (18.9% vs 8.8%) and dry eye (16.2% vs 11.8%).

Several large clinical studies to compare the efficacy of Botox® and Xeomin® have been reported. In comparative clinical trials, the efficacy and tolerability of Xeomin® were noninferior to that of conventional BoNT/A drugs.13,14 The efficacy of Xeomin® was compared with that of Botox® in a 16-week randomized, double-blind, noninferiority trial in 463 patients with cervical dystonia. Both treatments significantly improved the Toronto Western Spasmodic Torticollis Rating Scale severity score compared with baseline, and noninferiority of Xeomin® vs Botox® was demonstrated.14 Similarly, a randomized, double-blind study of Xeomin® and Botox® in 300 patients with blepharospasm found that both treatments significantly reduced JRS score from baseline, indicating noninferiority of Xeomin®.5,13 There was also no difference in the time course of the 2 treatments demonstrated in the Kaplan–Meier plot. There were no clinically relevant differences between Xeomin® and Botox® in safety parameters, 40 of 148 patients (27.0%) treated with Xeomin® reporting adverse events vs 45 of 155 patients (29.0%) treated with Botox®. The most common adverse event was ptosis (6.1% Xeomin® and 4.5% Botox®).5

In conclusion, the clinical evidence to date suggests that Xeomin® is an effective treatment for blepharospasm, which does not differ from Botox® in terms of its potency, duration of effect, or adverse reaction profile.5 The same efficacy and safety profiles could be explained by the immediate dissociation, which would lead to the generation of the same active agent, ie, the 150 kDa active neurotoxin, eliciting the same diffusion characteristics and therapeutic effects.

Dosing of Xeomin® should be based on previous Botox® treatment. If the previous information is not available, the recommended starting dose is 2.5 to 5.0 units per each injection site in blepharospasm.52 There is some evidence of a dose–response relationship for efficacy and its duration, in which the greatest benefits for Xeomin® were observed with the highest dose, and Dressler50 reported his experience of off-label indications and maximum therapeutic dose up to 840 units of Xeomin® as well as Botox® in a variety of muscle hyperactivity disorders without producing clinically detectable systemic adverse effects. However, few patients with blepharospasm received a total dose of greater than 75 units in the controlled trials and less than 70 units (35 U/eye) is recommended for initial total dose so far.52

Based on stability data, Xeomin® is the only preparation that remains active for up to 3 or 4 years at room temperature before reconstitution. In contrast, other botulinum toxin products require refrigerated storage.19,36,53,54 After reconstitution, Xeomin® should be stored for only 24 hours at 4°C, because otherwise sterility problems, such as bacterial contamination, could occur.11

**Conclusion**

Xeomin® was originally developed to reduce drug antigenicity, which can lead to partial or complete treatment failure. It recently became the fourth FDA-approved botulinum toxin drug in the US. A lack of complexing proteins differentiates Xeomin® from the other BoNT preparations. Many studies have also shown that Xeomin® has the same efficacy and safety profile as complexing protein-containing products such as Botox® and is exchangeable with Botox® using a simple 1:1 conversion ratio. Xeomin® represents a new treatment option for the repeated treatment of patients with blepharospasm in that it may reduce antibody-induced therapy failure. But, long-term, trials in naïve patients comparing Xeomin® with conventional BoNT/A drugs are required to confirm the low immunogenicity of Xeomin®.

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**Disclosure**

Dr Harrison is a paid consultant for Merz Pharmaceuticals.

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