The scientific study of botulinum toxin dates back to the 1800s, but it was not until the second half of the last century that human testing of therapeutic neuromodulators began and FDA-approved formulations came to market. Jürgen Frevert, PhD, led Botulinum Toxin Research at Merz Pharmaceuticals GmbH in Potsdam, Germany, starting in 2003. Dr. Frevert began studying botulinum toxins in 1983 and over the next 20 years worked for well-known manufacturers of therapeutic and aesthetic botulinum toxins. Among his research accomplishments, he purified and characterized all botulinum toxin serotypes (type A–type G) and developed assays and vaccines. During his early foray into the world of botulinum toxins, Dr. Frevert made an observation that puzzled him.

“I was surprised when I learned that the botulinum toxin products marketed at that time contained proteins that are unnecessary for treatment—some refer to these proteins as ‘complexing proteins.’ These bacterial proteins are completely unnecessary for effect,” Dr. Frevert says. “Since these proteins are unnecessary, why inject them into patients? Patients do not need these proteins.”

Dr. Frevert also wondered if the proteins could have unintended effects. “Based on my experience in the development of vaccines, I suspected that these proteins may have an effect on the immune system,” he says. “Therefore, I suggested developing a product free from these unnecessary proteins.”

It turns out the proteins are a defense mechanism of sorts for the Clostridia bacteria that produce the botulinum neurotoxin, and they play a critical role in the process of inducing botulism in humans who consume contaminated foods. The neurotoxin relies on the complexing proteins to survive the harsh conditions of the digestive tract. “The Clostridia essentially need the complexing proteins to cause botulism. In contrast, the complexing proteins play no role in the therapy when the neuromodulator is injected into the muscle to be treated,” Dr. Frevert explains.

As a bacterial protein, botulinum neurotoxin is an antigen, identified as a foreign protein to the immune system, Dr. Frevert points out. “But the immune system only forms antibodies against a foreign protein when it is activated by a danger signal, which is usually contributed by bacterial or viral components that act as adjuvant. Dendritic cells bind substances derived from bacteria or viruses and become thereby activated. This is the first and essential step in the activation of the immune system to produce antibodies.”

The neuromodulator itself does not bind to these cells, is not able to activate, and is therefore considered a weak antigen. However, the unnecessary proteins may contribute to the danger signal and act as an adjuvant, Dr. Frevert explains. “The activated cells then take up foreign material, including the neuromodulator, which results after further steps in the formation of antibodies against the neuromodulator. The unnecessary proteins are not necessary for the therapeutic effect, but they may play a part in the activation of the immune system.”

Given that antibodies can neutralize the activity of the neuromodulator, patients who develop them may become secondary non-responders. Dr. Frevert notes, “Antibody–induced treatment failure or a diminished response to botulinumtoxinA is reported in the treatment of neurological diseases with onabotulinumtoxinA or abobotulinumtoxinA, and a growing number of publications describe treatment failure in aesthetics, as well.”

One publication that analyzed titer levels in 560 patients found that 14 percent of patients who received a neuromodulator that contained unnecessary proteins developed secondary non-response or diminished response with continued exposure.

Ultimately, patients who develop immunogenicity to neurotoxins could require “a vacation” from therapy so titer levels can reduce to a point that they are able to have therapeutic response again. With all of this in mind, Dr. Frevert set out to formulate a botulinum neuromodulator formulation with no unnecessary proteins. The result is incobotulinumtoxinA, now marketed by Merz Aesthetics in the US as Xeomin. Dr. Frevert’s hunch appears to have been proven right. None of the more than 1,400 patients became secondary non-responders in all of Xeomin’s clinical studies across all indications. “No other botulinum toxin on the market can say that,” Dr. Frevert says. Plus, “Xeomin can be stored at room temperature, in contrast to other products, which must be kept refrigerated.”

Dr. Frevert came to the conclusion that if these additional proteins are unnecessary, have no impact on efficacy,
CLINICAL CONNECTION

WITH SHEILA BARBARINO, MD

Why did you start offering Xeomin? Why do you select it over other options?

I’ve used Xeomin since it came to market. I trusted the reputation Merz has for quality products, and I wanted to try a neuromodulator that was an alternative to what was then available.

I like Xeomin for a few key reasons. Other products have had patients develop decreased effect after multiple treatments. In clinical studies, Xeomin was consistently effective after multiple treatments/uses. I like that it is a uniquely purified protein.

As an oculoplastic surgeon, as an ophthalmologist, I treat blepharospasm. I see resistance often. People argue that in cosmetics you don’t use amounts high enough to create resistance. But that’s not true. Resistance is related not only to dosing but also to duration of use. I’ve seen resistance in cosmetic patients. Now that we’re coming up to almost 20 years of cosmetic neuromodulator usage, we’re seeing a lot more resistance in cosmetic patients, because they have used it for so many years.

What benefits does Xeomin offer to your practice? For patients?

For my patients in their twenties and thirties receiving a preventative neuromodulator, I feel like it’s my duty as a doctor to start with Xeomin, because the longer you use a neuromodulator, evidence suggests, there is a greater chance of developing resistance. I think it’s important, especially for those younger millennials, to start off with Xeomin; when they’re 60 years old, it may be more likely that I can still treat them with a neuromodulator versus them being resistant at that point. Plus, we also have to keep in mind that these younger patients could one day develop medical conditions that require therapeutic neuromodulator treatment, and we don’t want to increase the risk of developing resistance from cosmetic use.

Because of the competitive pricing of Xeomin, I can pass savings onto my patients, and many of them then spend money in my practice on other things.

I also feel that I can achieve a natural looking, non-frozen appearance with Xeomin. That matters to patients, especially those new to neuromodulators. They’re often afraid of looking too frozen. That said, if someone wants a more frozen appearance, I can achieve that with Xeomin, too.

You mentioned the purity of Xeomin. Is that something that resonates with patients?

Patients don’t generally ask about purity, and I don’t think that most patients really understand neutralizing antibodies. I think that’s a problem. I also think, unfortunately, some injectors don’t really know the ramifications of neutralizing antibodies. I think that it’s really important that I’ve been positioned to educate our extenders, our nurses, our injectors, and our patients about neutralizing antibodies.

Once they understand the options, many patients find the notion of a uniquely purified product appealing.

Although individual results vary, my patients have been extremely happy with Xeomin results, whether they like a frozen look or whether they like a natural appearance. They like that it’s a uniquely purified product without unnecessary proteins. They like that the price is a little bit of a price break for them, because then they can come back to have their fillers or their lasers that they want in addition to just having the neuromodulator. And on top of that it’s just a great product. Patients are really happy. That’s why I inject myself with Xeomin. That’s why I inject my family members with Xeomin.

4. Xeomin Prescribing Information, Merz Aesthetics.
INDICATIONS AND USAGE

XEOMIN® (incobotulinumtoxinA) for injection, for intramuscular use is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adult patients.

IMPORTANT SAFETY INFORMATION

WARNING: DISTANT SPREAD OF TOXIN EFFECT
See full prescribing information for complete BOXED WARNING.

The effects of XEOMIN and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults, particularly in those patients who have underlying conditions that would predispose them to these symptoms.

CONTRAINDICATIONS

Hypersensitivity reactions have been reported with botulinum toxin products (anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea). If serious and/or immediate hypersensitivity reactions occur further injection of XEOMIN should be discontinued and appropriate medical therapy immediately instituted. XEOMIN is contraindicated in patients with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

Use in patients with an infection at the injection site could lead to severe local or disseminated infection. XEOMIN is contraindicated in the presence of infection at the proposed injection site(s).

WARNINGS AND PRECAUTIONS

- The potency units of XEOMIN are specific to the preparation and assay method used and are not interchangeable with other preparations of botulinum toxin products. Therefore, Units of biological activity of XEOMIN cannot be compared to or converted into Units of any other botulinum toxin products.

- Treatment with XEOMIN and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. When distant effects occur, additional respiratory muscles may be involved. Patients may require immediate medical attention should they develop problems with swallowing, speech, or respiratory disorders. Dysphagia may persist for several months, which may require use of a feeding tube. Aspiration may result from severe dysphagia [See BOXED WARNING].

- Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from typical doses of XEOMIN.
• **Glabellar Lines:** Do not exceed the recommended dosage and frequency of administration of XEOMIN. In order to reduce the complication of ptosis the following steps should be taken:
  - avoid injection near the levator palpebrae superioris, particularly in patients with larger brow depressor complexes;
  - corrugator injections should be placed at least 1 cm above the bony supraorbital ridge.

• **XEOMIN** contains human serum albumin. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been reported for albumin.

**ADVERSE REACTIONS**

**Glabellar Lines:** The most commonly observed adverse reaction (incidence ≥ 2% of patients and greater than placebo) for XEOMIN was Headache (5.4%).

**DRUG INTERACTIONS**

Co-administration of XEOMIN and aminoglycoside or other agents interfering with neuromuscular transmission, (e.g., muscle relaxants), should only be performed with caution as these agents may potentiate the effect of the toxin.

Use of anticholinergic drugs after administration of XEOMIN may potentiate systemic anticholinergic effects. The effect of administering different botulinum toxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

**USE IN PREGNANCY**

There are no adequate data on the developmental risk associated with the use of XEOMIN in pregnant women. XEOMIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**PEDIATRIC USE**

Safety and effectiveness of XEOMIN in patients less than 18 years of age have not been established.

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