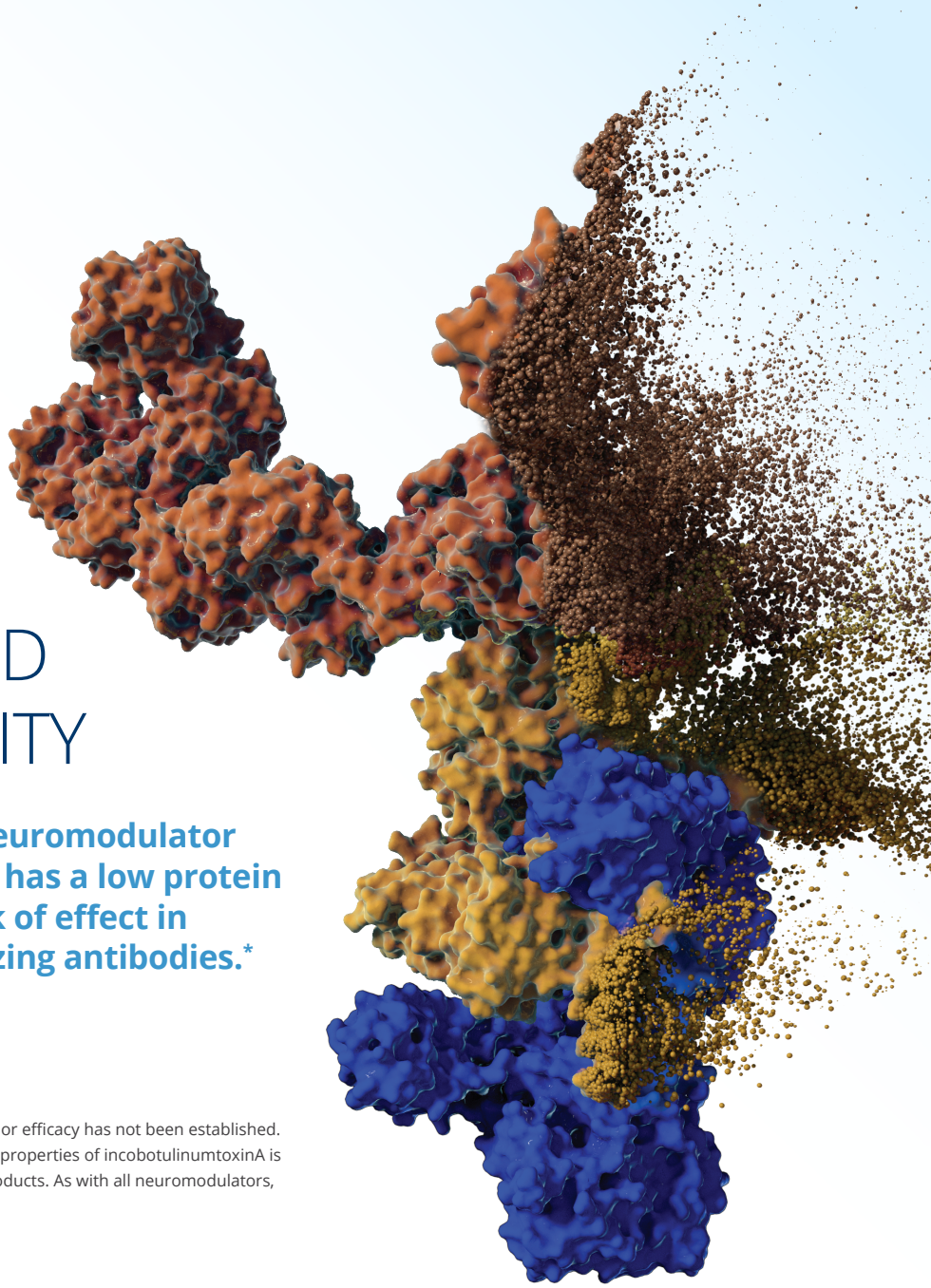
XEOMIN®
incobotulinumtoxinA



NEUTRALIZING ANTIBODIES AND IMMUNOGENICITY

XEOMIN, a uniquely purified neuromodulator without unnecessary proteins, has a low protein load and demonstrated no lack of effect in clinical studies due to neutralizing antibodies.*

*The direct impact of the non-therapeutic proteins on long term safety or efficacy has not been established. Information about the unique XEOMIN manufacturing process and the properties of incobotulinumtoxinA is not intended to imply superiority over other botulinum toxin type A products. As with all neuromodulators, including XEOMIN, there is a potential for immunogenicity.

IMPORTANT SAFETY INFORMATION

INDICATIONS

XEOMIN® (incobotulinumtoxinA) for injection is indicated for the treatment of:

- Chronic sialorrhea in patients 2 years of age and older
- Upper limb spasticity in adults
- Upper limb spasticity in pediatric patients 2 years of age and older, excluding spasticity caused by cerebral palsy
- Cervical dystonia in adults
- Blepharospasm in adults

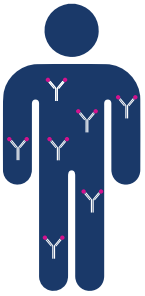
WARNING: DISTANT SPREAD OF TOXIN EFFECT
See full prescribing information for complete BOXED WARNING.

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.

See additional Important Safety Information on pages 7 and 8.

Please see accompanying Full Prescribing Information, including BOXED WARNING.

Potential Causes for Immunogenicity



Development of neutralizing antibodies

- A higher protein load increases your patient's risk of developing neutralizing antibodies

No head-to-head studies have been conducted on the likelihood of developing neutralizing antibodies between or among botulinum toxin products.

- Formation of neutralizing antibodies can lead to clinical resistance

Repeated exposure to treatment

- Higher cumulative doses and repeated exposure to treatment of botulinum toxin could increase the immune response

Consider the potential for immunogenicity when choosing a treatment for your patients*

Potentially minimize immune response to decrease the chances for loss of clinical benefit*

No long-term studies have been conducted to assess the potential impact of neutralizing antibodies in patients over several years of therapy.

*As with all neuromodulators, including XEOMIN, there is the potential for immunogenicity.

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS

- Known hypersensitivity to any botulinum toxin product or to any of the components in the formulation.
- Infection at the proposed injection site(s) because it could lead to severe local or disseminated infection.

WARNINGS AND PRECAUTIONS

- Serious 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, discontinue further injection of XEOMIN and institute appropriate medical therapy immediately. The use of XEOMIN in patients with a known hypersensitivity to any botulinum neurotoxin or to any of the excipients (human albumin, sucrose), could lead to a life-threatening allergic reaction.
- 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]*.

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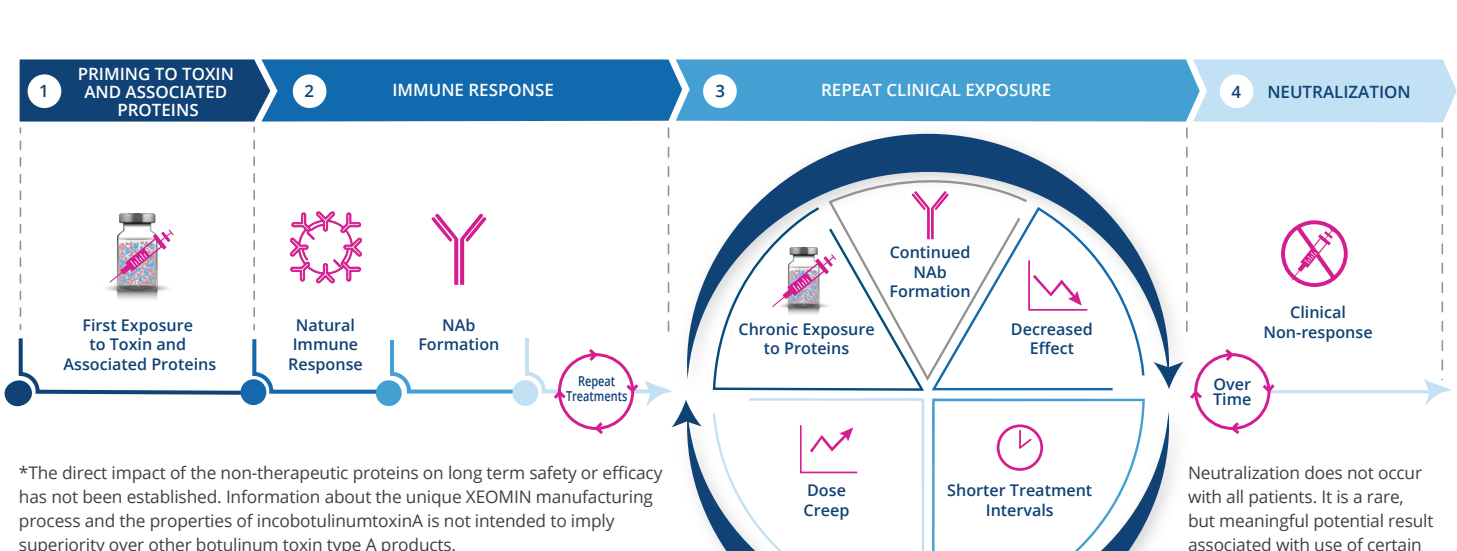
The Neurotoxin Immune Response Cycle[1-8]

Peer-Reviewed Journal Articles Establish Treating Patients With Neurotoxins That Have Unnecessary Proteins Can Lead To*†:



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†Development of neutralizing antibodies is possible with all botulinum toxin formations, including XEOMIN.

Neutralization does not occur with all patients. It is a rare, but meaningful potential result associated with use of certain proteins over time.

Learn more about XEOMIN and the immune response cycle at **XEOMIN.COM**

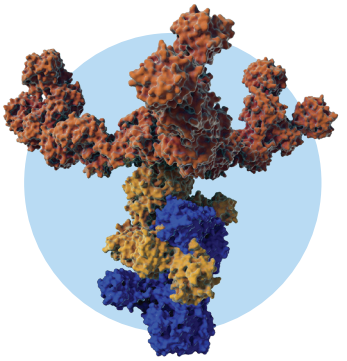
IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

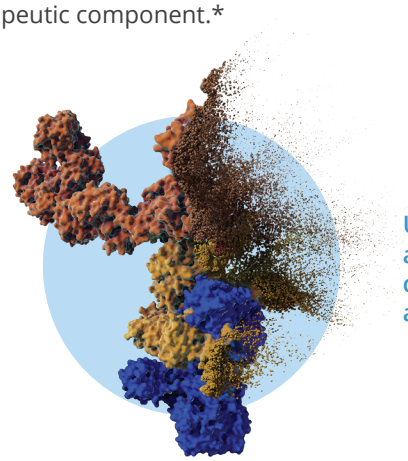
- Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) may be at increased risk for severe dysphagia and respiratory compromise from typical doses of XEOMIN.
- **Cervical Dystonia:** Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been post-marketing reports of serious breathing difficulties, including respiratory failure, in patients with cervical dystonia treated with botulinum toxin products. Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscles are at greater risk of dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may decrease the occurrence of dysphagia.
- **Blepharospasm:** Injection of XEOMIN into the orbicularis oculi muscle may lead to reduced blinking and corneal exposure with possible ulceration or perforation. To decrease the risk for ectropion, XEOMIN should not be injected into the medial ower eyelid area.

Uniquely Purifying Botulinum Toxin Type A Into XEOMIN

XTRACT Technology™ is the only state-of-the-art manufacturing process that uniquely purifies the molecule removing the unnecessary proteins, leaving just the active therapeutic component.*



Botulinum toxin type A is produced in Hall strain Clostridium botulinum stereotype A[9]



Unnecessary proteins are separated by chromatography, producing a purified molecule

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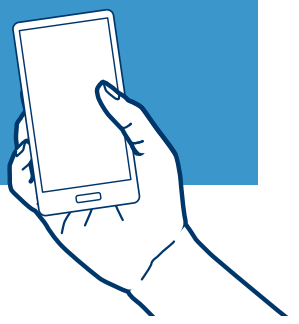
See how XEOMIN is uniquely purified with XTRACT Technology™



IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

- 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

The most commonly observed adverse reactions at rates specified below and greater than placebo are:

- **Chronic Sialorrhea:**
- **in adults** (≥4% of patients): tooth extraction, dry mouth, diarrhea, and hypertension.
- **in pediatric patients** (≥1% of patients): bronchitis, headache, and nausea/vomiting.
- **Upper Limb Spasticity:**
  - **in adults** (≥2% of patients): seizure, nasopharyngitis, dry mouth, and upper respiratory tract infection.
  - **in pediatric patients** (≥3% of patients): nasopharyngitis and bronchitis.

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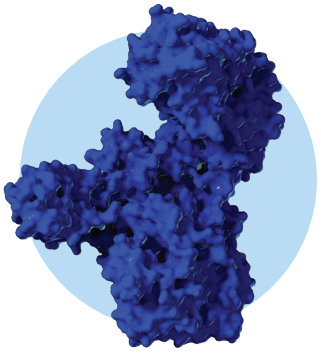
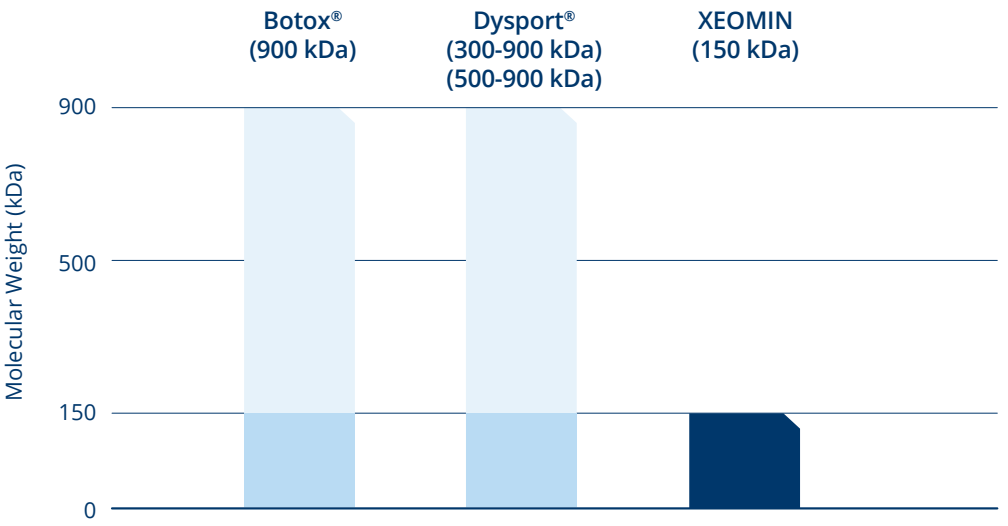
XEOMIN Is the Only Clinically Proven Neuromodulator Uniquely Purified to Remove Unnecessary Proteins



150 kDa XEOMIN Molecule[10]

XEOMIN has a molecular weight of 150 kDA and is formulated to have a high biological activity with a low bacterial protein load

Molecular Weights of Botulinum Toxins[10]



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.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

- **Cervical Dystonia in adults** (≥5% of patients): dysphagia, neck pain, muscle weakness, injection site pain, and musculoskeletal pain.
- **Blepharospasm in adults** (≥10% of patients): eyelid ptosis, dry eye, visual impairment, and dry mouth.

DRUG INTERACTIONS

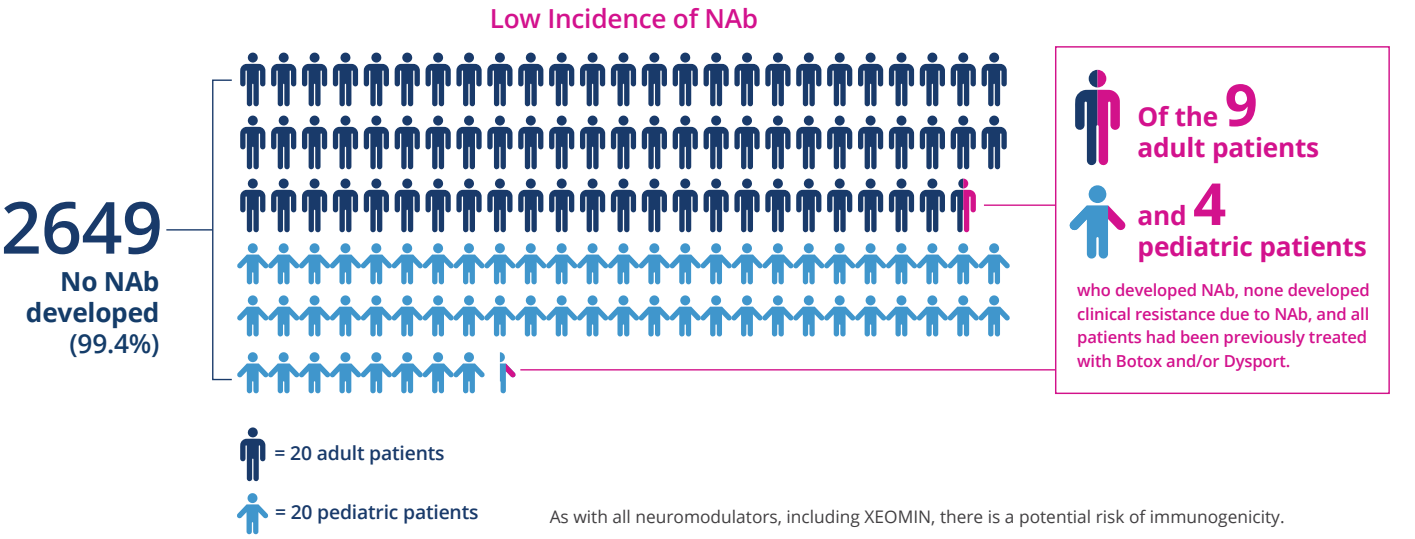
Co-administration of XEOMIN and aminoglycoside or other agents interfering with neuromuscular transmission, (e.g., muscle relaxants), should only be performed with caution as these agents may potentiate the effect of the toxin.

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.

XEOMIN Patients Did Not Develop Clinical Resistance Due to Neutralizing Antibodies (NAb) in Clinical Studies

Of the 2650 patients treated with XEOMIN in clinical trials, no patients demonstrated clinical resistance or secondary treatment failure due to NAb.



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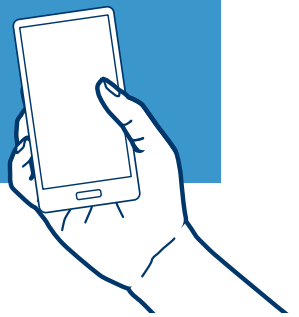
Hear an immunologist discuss immunogenicity and XEOMIN clinical data



IMPORTANT SAFETY INFORMATION (continued)

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 for lower limb spasticity, cervical dystonia, or blepharospasm.

Safety and effectiveness have been established in pediatric patients 2 to 17 years of age in patients with chronic sialorrhea and upper limb spasticity. A pediatric assessment for XEOMIN in upper limb spasticity demonstrates that XEOMIN is safe and effective in another pediatric population. However, XEOMIN is not approved for such patient population due to marketing exclusivity for another botulinum toxin.

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IMPORTANT SAFETY INFORMATION (continued)

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References: 1. Yablon SA, Breshear A, Gordon MF, et al. *Clin Ther.* 2007;29(4):683-90. **2.** Marcelissen T, Cornu JN, Antunes-Lopes T, et al. *Eur Urol Focus.* 2018;4(5):760-767. **3.** Dessler D. *Mov Disord.* 2004;19 Suppl 8:S92-S100. **4.** Jankovic J, et al. *Neurology.* 2003;60(7):1186-8. **5.** Naumann M, et al. *J Neural Transm.* 2013;120(2):275-290. **6.** Benecke R. *BioDrugs.* 2012;26(2):e1-9. **7.** Hefter H. *BMJ Open.* 2012;2(4).pii:e000646. **8.** Mathevon, et al. *Annals of Physical and Rehabilitation Medicine.* 62(2019) 241-251. **9.** XEOMIN® [Package insert]. Raleigh, NC: Merz Pharmaceuticals, LLC; 2021. **10.** Dressler D, Benecke R. Pharmacology of therapeutic botulinum toxin preparations. *Disabil Rehabil.* 2007;29(23):1761-1768.

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