Consensus Panel’s Assessment and Recommendations on the Use of 3 Botulinum Toxin Type A Products in Facial Aesthetics

Z. Paul Lorenc, MD; Jeffrey M. Kenkel, MD; Steven Fagien, MD; Haideh Hirmand, MD; Mark S. Nestor, MD, PhD; Anthony P. Sclafani, MD; Jonathan M. Sykes, MD; and Heidi A. Waldorf, MD

Abstract
In this summary article, the authors discuss the characteristics of abobotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA. With 3 neuromodulators available in the US market, comparisons between and among products will invariably be made, so arguments for the most effective facial aesthetic uses of each neuromodulator are presented. Topics addressed in this article include patient expectations, toxin reconstitution and preparation, patient positioning, differences among products, the role of complexing proteins, and dosing and injection strategies. Recommendations are also provided by treatment area.

Keywords
facial aesthetics, glabellar lines, neuromodulators, neurotoxins, Botox, onabotulinumtoxinA, Dysport, abobotulinumtoxinA, Xeomin, incobotulinumtoxinA, botulinum neurotoxin type A

Accepted for publication March 21, 2012.

Although previous clinical recommendations have been published on the use of onabotulinumtoxinA and abobotulinumtoxinA, many of these articles have addressed only 1 product. For example, a supplement from Plastic and Reconstructive Surgery addressed only onabotulinumtoxinA, since it was the sole botulinum toxin type A approved for facial aesthetics at the time of publication. The authors of those articles discussed aesthetic evaluation and treatment, handling and reconstitution, dosing and injection-site variables, and techniques for each treatment area. A previous supplement in Aesthetic Surgery Journal focused on abobotulinumtoxinA; the authors examined pivotal clinical trials of the product for safety and efficacy, discussed the drug manufacturing process, and provided a clinical indications and practice guide for physicians. In a Journal of Drugs in Dermatology supplement, the consensus panel’s assessment and recommendations addressed clinical trials for facial aesthetics, similarities and differences between onabotulinumtoxinA and abobotulinumtoxinA, dose ranges for abobotulinumtoxinA, and facial anatomy considerations.

The introduction of a third botulinum toxin type A (BoNTA) in the United States, incobotulinumtoxinA (Xeomin; distributed by Merz Aesthetics Inc and Merz Pharmaceuticals LLC, Greensboro, NC. Xeomin is also

Dr Lorenc is a plastic surgeon in private practice in New York, New York. Dr Kenkel is Professor and Vice Chairman of the Department of Plastic Surgery at the University of Texas Southwestern Medical Center at Dallas in Dallas, Texas, and he is Associate Editor of Aesthetic Surgery Journal. Dr Fagien is a plastic surgeon in private practice in Boca Raton, Florida. Dr Hirmand is Assistant Clinical Professor at Weill-Cornell Medical College, New York, New York. Dr Nestor is Voluntary Associate Professor in the Department of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine, Miami, Florida. Dr Sclafani is Director of Facial Plastic Surgery and Professor of Otolaryngology–Head and Neck Surgery, Facial Plastic Surgery, at The New York Eye and Ear Infirmary, New York, New York. Dr Sykes is Director of Facial Plastic and Reconstructive Surgery, UC Davis Medical Center, Sacramento, California. Dr Waldorf is Associate Clinical Professor of Dermatology at Mount Sinai School of Medicine, New York, New York.

Corresponding Author:
Dr Z. Paul Lorenc, 983 Park Avenue, New York, NY 10028, USA. E-mail: lorenc@lorenc.com
known by the tradename Bocouture for aesthetics use outside of the US), makes the need for updated recommendations even more salient. Rather than focus on incobotulinumtoxinA alone, this supplement considers all 3 BoNTA products and provides updated information on the use of BoNTA products for enhancement of facial aesthetics. As noted in the Introduction, a group of experts from facial plastic surgery, oculoplastic surgery, plastic surgery, and dermatology gathered on November 30, 2011, in New York to review the use of BoNTA products in the United States and to develop clinical recommendations. These guidelines summarize key discussions from the meeting and provide recommendations for the aesthetic use of BoNTA.

The application of BoNTA for aesthetic purposes is driven by general principles common to all 3 BoNTA products as well as unique characteristics of each toxin product. Specific product profiles, including extensive coverage of efficacy and safety studies, are detailed in other articles in this supplement. This consensus article includes discussion of overall clinical considerations, including aesthetic considerations and techniques to maximize patient satisfaction, reconstitution/handling, dosage, anatomy, and information specific to common injection sites.

**Aesthetic Considerations**

BoNTA products are approved in the United States for the correction of glabellar lines and are used for other off-label aesthetic indications in the face, including, but not limited to, crow’s feet, perioral lines, and horizontal forehead lines. Although each of the 3 products can be used with similar effect and duration and, in the opinion of the authors, are remarkably similar, an awareness of the differences, particularly related to dosing and reconstitution, is critical. These topics are discussed later in this article.

**Patient Expectations**

Once a patient is considered a likely candidate for BoNTA injections, an overall treatment plan that takes into account the patient’s short- and long-term goals should be developed. The desired overall effect should also be discussed with patients (eg, gentle relaxation vs a more dramatic effect). Realistic expectations about the effectiveness of BoNTA injections for each patient (and each treatment site) should also be discussed, as well as expected duration of action. Of course, not all patients will be candidates for BoNTA. Physicians should be empathetic with such patients regarding their aesthetic goals but also clear and realistic.

All patients should have an understanding of the role of toxins versus other dermal products such as injectable fillers and laser resurfacing, both of which may be part of an overall treatment strategy that includes BoNTA injections. The authors’ consensus is that, in most circumstances, it is effective to use BoNTA and a filler or volumizing agent on the same day. However, the treatments may also be separated into 2 visits for cost-conscious patients or for other reasons. Certain procedures, though, may not be considered appropriate for same-day treatment with neuromotors. For example, the authors do not recommend skin resurfacing on the same day; ideally, laser resurfacing would occur after BoNTA injections because the skin surface is more even and quiescent posttreatment, thereby providing a more even distribution of light energy. Although there is not universal consensus on this, the authors usually perform surgery first in a neurotoxin-naïve patient, then treat with neurotoxin. This practice ensures neutral position of the tissues (eg, the brow position in a browlift) when formulating a surgical strategy. It also allows for the appropriate amount of skin excision during a procedure such as blepharoplasty. Neurotoxins can be administered following surgery to produce a more predictable result.

As the market for neurotoxin products increases and the time since onabotulinumtoxinA’s introduction lengthens, more patients have had experience with BoNTA products. Indeed, some of them may enter a practice after having had negative experiences elsewhere. Some injectors use overdiluted product or insufficient dosages; others inject too much and often in suboptimal areas of the face. The authors recommend starting reluctant patients with small corrections or focused areas of treatment first. If such corrections are satisfactory to the patient, expansion of treatment to other areas of the face may be appropriate. Setting expectations is also critically important. Clinicians should not set expectations too high; instead, it is often better to “underpromise and overdeliver.”

In the era of intense marketing, there are a range of expectations set for neuromodulators. In an effort to gain patients, information may not be accurately depicted or may be incorrectly perceived. The safety of BoNTA may be over- or understated. In addition, patients are also often confused by the differences in indications and physical properties among BoNTA products as well as with dermal fillers.

Before the BoNTA injection procedure, the risks, benefits, and possible complications of treatment should be discussed with the patient. Informed consent documents should be reviewed, signed, and placed in the patient’s medical record. Neurotoxin product labeling requires that printed patient information materials produced by the manufacturer be given directly to the patient, and this process should be duly noted in the medical record.

Patient photographs may be taken to facilitate patient and injector satisfaction with treatment and to enhance communication. The authors recommend photographs be taken before any first-time procedure for each patient and again approximately 2 weeks after treatment. Since the full onset of action occurs approximately 10 to 14 days posttreatment,6 evaluation at 2 weeks usually is ideal. Beyond this point, there is diminishing noticeable change. Given that many patients’ natural inclination would be not to return until 3 to 4 months (once the effects of the toxin have begun to wear off and repeat treatment likely becomes appropriate), the authors suggest scheduling the 2-week follow-up appointment before the patient leaves the clinical setting, especially for first-time patients who
need to be photographed and evaluated. For repeat patients receiving injections for previously treated indications, periodic photographs may suffice; this decision should be based on physician familiarity with the patient and previous results.

**TOXIN RECONSTITUTION AND PREPARATION**

Each of the products is reconstituted with a 0.9% sterile, preservative-free saline solution, drawn up with a 1-inch 22-gauge or 26-gauge needle. Although official product labeling calls for preservative-free saline (not only because alcohol can, in theory, affect the toxin but also because the pivotal trials were performed using preservative-free saline), preserved saline may be used to reduce patient pain. The consensus, based mostly on anecdotal experience, is that a small amount of preservative used in reconstitution is not sufficient to affect toxin integrity, and preserved saline has an advantage of reducing pain by providing an anesthetic effect.6,7 Although product labeling for all 3 BoNTA products calls for the immediate use of reconstituted product, the panel’s consensus is that reconstituted BoNTA may be refrigerated for up to 6 weeks and safely used during that time without a notable change in product integrity and efficacy.8

The volume of saline used depends on the desired concentration the clinician wishes to obtain from each vial. For onabotulinumtoxinA and incobotulinumtoxinA, most members of the panel reconstitute with 2 to 2.5 mL per 100-U vial; 3 of the panel members use as much as 4 mL per 100-U vial. For abobotulinumtoxinA, the corresponding reconstitution noted among the panel members is generally between 1.5 and 3 mL per 300-U vial.

**POSITIONING**

The patient should be seated in an examination chair reclined approximately 60 to almost 90 degrees. Although many injectors work successfully with the patient at near 90 degrees, the advantage of a greater angle is that it allows the patient to relax and lie back, while stabilizing his or her head so that the patient still maintains a vertical orientation. Ideally, the chair height should be such that the patient’s head is at shoulder level with the injector.

**PRODUCT DIFFERENCES**

The review articles from this supplement discussing each of the 3 products (plus the extensive literature review of incobotulinumtoxinA) provide important information about the use, safety, and efficacy of each. It is the general opinion of the authors, however, that no one product is demonstrably superior to the others, nor is any one of them a clearly inferior choice. In the panel’s experience and reading of the literature, the volume used, dilution amount, and injection technique (among other factors) affect outcome more than simply selecting one product over another. Indeed, physicians will likely find themselves favoring certain products for certain indications. Some of the panel members find, for example, that abobotulinumtoxinA is more favorable for softer transitions from treated versus nontreated areas, whereas onabotulinumtoxinA or incobotulinumtoxinA is more appropriate for more discrete zones of action. Although there are studies that claim superiority of one product or another, the panel finds that these studies are generally underpowered and/or potentially biased by funding from manufacturers. Such studies also highlight relative differences in efficacy based on ratios of units rather than differences in the toxins themselves. Although the differences between products may be slight, they generally are not clinically relevant.

A study published in 2003 compared BoNTA and botulinum toxin type B (BoNTB) for the reduction of rhytids in the periorcular area and concluded similar efficacy between the 2 products, although BoNTB was found to be associated with nonclinical outcomes such as slightly increased discomfort upon injection.9 Two recent studies are exemplary of the type of differences when 2 BoNTA products are compared with each other. In a study by Prager et al10 comparing onabotulinumtoxinA and incobotulinumtoxinA for the correction of crow’s feet, 12 U of either product achieved similar results. A study by Nestor and Ablon11 compared abobotulinumtoxinA with onabotulinumtoxinA and found slightly faster onset and longer efficacy with abobotulinumtoxinA, but this was when a 2.5:1 abobotulinumtoxinA to onabotulinumtoxinA ratio was used. Had a 2:1 ratio been used, more similar results would likely have been expected.

The panel members note that, although the way units are measured is proprietary to each company, all 3 products are remarkably similar in efficacy and safety. Differences among the 3 products, in our opinion, are perhaps overdiscussed. This means that selection is subject to other, less objective factors: personal preferences, experiences with each product over time, and cost considerations.

**ROLE OF COMPLEXING PROTEINS**

IncobotulinumtoxinA is distinguished from the 2 other BoNTA products by its lack of complexing proteins. The molecular structure of BoNTA is discussed in the incobotulinumtoxinA overview elsewhere in this supplement, but to summarize, the amount of neurotoxin product as well as complexing proteins and residual proteins together define the foreign protein load. The human immune system may recognize any part of this protein load as a foreign substance and trigger an immune reaction after injection.

Studies have suggested that a higher total protein content might contribute to a greater chance of antibody formation.11,12 As a result, the evolution of BoNTA products has corresponded to a reduction of the total protein content. The original onabotulinumtoxinA formulation contained...
25 ng of neurotoxin complexing proteins per 100 U, whereas the current formulation contains only 5 ng of complexing proteins per 100 U.\textsuperscript{13} Patients treated with the original formulation of onabotulinumtoxinA (before 1998) were 6 times more likely to have blocking antibodies than those who received the newer formulation.\textsuperscript{14} In a study of 130 patients treated for cervical dystonia with onabotulinumtoxinA, laboratory samples of 4 of the 42 (9.5%) patients treated with original onabotulinumtoxinA had detectable blocking antibodies, but no laboratory samples of the 119 patients treated exclusively with current onabotulinumtoxinA manifested detectable blocking antibodies.\textsuperscript{14}

Nevertheless, there are sometimes cases in which patients do not respond to neurotoxins. Factors such as genetics may play a role. Once the possibility of underdosing is excluded, an immune response is suspected. BoNTB sometimes has been used in these cases. Anecdotal experience with patients suspected of developing an immune response to onabotulinumtoxinA leads the panel to posit that such patients might experience a favorable response with incobotulinumtoxinA. In cases such as these, in patients with a suspected immune response to onabotulinumtoxinA, the need for thoughtful patient counseling and thorough documentation before proceeding with a different neuromodulator is strongly advised. Another strategy members of the consensus panel use to avoid immune response is to administer smaller, more frequent doses so that the body may adapt over time. Larger doses may be more likely to stimulate an immune response.

Some authors have posited that incobotulinumtoxinA’s lack of complexing proteins may be a disadvantage because the smaller size of incobotulinumtoxinA might more easily diffuse away from target tissue and into adjacent tissues, producing an adverse event profile different from other BoNTA products. Clinical studies, however, do not support this hypothesis. A study of onabotulinumtoxinA, abobotulinumtoxinA, and a purified preparation of BoNTA (150 kDa) showed that diffusion from the injection site did not differ among the 3 preparations.\textsuperscript{15} Another study showed no difference in the diffusion of the free or complexed form of BoNTA after injection into the muscle, even at high doses.\textsuperscript{16} The topic of diffusion, particularly as related to abobotulinumtoxinA compared with onabotulinumtoxinA, is discussed in the review article about abobotulinumtoxin found elsewhere in this supplement.

### DOSING AND STRATEGIES FOR INJECTION SITES

The following section contains information about specific dosages and, when applicable, injection techniques used by the authors for certain sites. Notice that there is a certain range of opinions among the panel, reflecting the variation of dosages and strategies that can be used to achieve successful results. Doses given are for onabotulinumtoxinA or incobotulinumtoxinA; approximate dosages for abobotulinumtoxinA can be determined using a 2:1 or 2.5:1 conversion ratio.

### Glabellar Lines

Product labeling recommends 20 U of onabotulinumtoxinA or incobotulinumtoxinA, generally divided into 5 equal injection points. Members of the consensus panel use approximately this dosage, although several of the panel members start with smaller dosages, such as 10 to 15 U, with higher dosages for those with stronger muscle mass (30-40 U). To minimize the risk of lid and/or brow ptosis, it is important to inject more superficially at the tail of the corrugator or at the subdural insertion points and somewhat deeper (intramuscularly) at the more medial body of the corrugator muscles based on frown pattern.

### Crow’s Feet

Members of the consensus panel inject 8 to 16 U on each side of the face. This total dose is divided by the number of planned injection points, usually 4 on each side. Any regional veins should be noted and avoided. Some of the authors prefer to use magnifying lenses to better visualize these vessels. It is extremely important to inject superficially in this area to avoid or minimize bruising. The needle should be oriented away from the orbit.

### Lower Eyelid

The panel members treat this area very selectively, because injecting toxin in this area can make the eyelid look worse in some patients. To enhance the appearance of the eyes, many patients may benefit from enlarging the aperture. If the lower eyelid is to be treated, the panel recommends starting with a dosage of 0.5 U/eyelid and injecting centrally at the junction between the tarsal and orbital orbicularis (Figure 1). Total dosage may be 0.5 to 2.5 U, maximum. Note that the pattern of squint and smile, as well as pretarsal and orbital orbicularis recruitment, is an important indicator to determine location of injection. Dry eyes, scleral show, and loose lower lids are red flags and should alert the injector to the possibility of problems with the treatment of the lower eyelid with BoNTA. In such cases, BoNTA should be avoided, or lower dosages of 0.5 U/eyelid injected at the most lateral point should be considered.

### Horizontal Forehead Lines

The frontalis muscle elevates the brow; its contraction is associated with the development of horizontal forehead lines. Treating the frontalis can be daunting for less experienced injectors. One wants to treat forehead lines while also maintaining some movement of the frontalis muscle to avoid paralysis and a “frozen” appearance. Another risk of treating the frontalis is eyebrow ptosis, which can result even while still failing to treat lines. The consensus panel recommends that, if the frontalis is to be treated, the glabella must also be treated, thus treating both the elevators and the depressors.
In some patients, such as those who recruit their frontalis to keep brows elevated or those with short foreheads, any treatment of the frontalis may lead to brow ptosis, even if the glabella is also treated. Isolated treatment of the frontalis should be considered only in unique scenarios.

The number of injection sites can vary significantly, although most injectors use 4 to 6 sites. It is important that all injections remain 1 to 2 cm above the orbital rim to decrease the risk for brow ptosis. For some injectors, the upper two-thirds of the forehead is considered a “safe zone.” Finally, in some patients, filler may be needed to soften lines in areas where toxin should be avoided and/or to augment the effects of BoNTA. Total starting dosages generally are 10 to 20 U for women and may be doubled for men depending on the muscle mass observed, although some injectors have used as few as 2 to 4 U, particularly for women.

**Lips**

Smoking, aging, and habitual facial expressions can result in changes to the appearance of the lips, particularly the formation of vertical perioral rhytids. BoNTA can improve the appearance of wrinkles in this area. Dosage for the perioral area among the panel is 5 U total (2.5 U on each side). The number of injection sites varies. In general, injections should be kept symmetrical and superficial. The patient’s pattern of recruitment of the orbicularis oris (or the “pout” pattern) can help guide the location of injections. In addition, patient outcome is often enhanced when BoNTA is combined with fillers and/or resurfacing treatment in this area.

**Dimpled Chin**

The appearance of a dimpled chin can be reduced with the use of BoNTA, although toxin is best used conservatively in this area. Members of the consensus panel most often inject a total of 4 to 5 U, with 2 injection sites (1 on each side) at the jawline or slightly superior to the jawline.

**Depressor Anguli Oris**

The depressor anguli oris (DAO) depresses the mouth angle and pulls down on the oral commissures to create marionette lines from the corners of the mouth to the jaw; these can be particularly troubling as patients age. Weakening the DAO with BoNTA minimizes downward pull on the dermal insertions of the muscle and can raise the oral commissures. Members of the consensus panel recommend, on average, 2.5 U per side.

**Platysmal Bands**

Although BoNTA is used by some physicians to treat platysmal bands of the neck, the consensus panel agrees that the use of BoNTA for this indication may produce variable results and may pose a relatively high risk for adverse events (including dysphagia due to local toxin spread) or indiscernible results, in part because of patient expectations. Thus, many of the panel members feel that BoNTA in the neck should be used with caution and only in appropriately selected patients. Those with good skin elasticity and minimal submental fat are good candidates, and these patients are usually relatively younger.

**CONCLUSIONS**

By choosing patients selectively and educating them about the benefits and limitations of BoNTA, physicians can increase the likelihood of optimal results with neurotoxin products. As this summary of the panel discussion suggests, a number of strategies, reconstitution techniques, dosages, and injection sites can be employed to maximize results. No single technique works for all injectors and in all patients. Given the addition of a third BoNTA product into the American market, the panel encourages physicians to take advantage of these choices and to become comfortable with using all 3 BoNTA products—to “mix and match” based on comfort, experience, and outcomes with each product. The panel is excited by the new choice afforded by incobotulinumtoxinA and the possible reduction in price that a more competitive toxin market may spur.

**Acknowledgments**

The authors acknowledge the editorial and writing assistance of Mark R. Vogel, MA, and David J. Howell, PhD, medical communications specialists in San Francisco, California, as well as assistance in the development of graphics from Bill Winn, an illustrator in Atlanta, Georgia.
Disclosures

Dr Lorenc is a paid consultant for Mentor, Merz Aesthetics, Medicis, and Johnson & Johnson. Dr Fagien is an advisory board member and paid investigator for Allergan, Medicis, Merz Aesthetics, and Galderma. Dr Hirmand is a speaker for Medicis Aesthetics, an advisory board member for Merz Aesthetics, and a paid investigator for Invasix. Dr Nestor is an advisory board member for Medicis, Merz Aesthetics, Galderma, Compulink, and Allergan. Dr Sclafani is a paid consultant and grant recipient for Aesthetic Factors. Dr Sykes is an advisory board member for Mentor and Allergan and a member of the speakers bureau for Sanofi-Aventis and Medicis. Dr Waldorf is an advisory board member, paid consultant, and speakers bureau member for Merz Aesthetics, Medicis, Allergan, Valeant, Solta, Bropelle, P&G, Johnson & Johnson, Unilever, and Rhythera. Unless otherwise noted, the faculty and planners have nothing to disclose. Editorial and writing assistance for this manuscript was provided by Medical Education Advocates.

Funding

This supplement was funded by an unrestricted educational grant from Merz Aesthetics, the maker of one of the products discussed in these articles.

REFERENCES