

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

ABBVIE INC.,
1 North Waukegan Road
North Chicago, IL 60064;

Plaintiff,

v.

U.S. DEPARTMENT OF HEALTH AND HUMAN
SERVICES,
200 Independence Avenue, S.W.
Washington, DC 20201;

CENTERS FOR MEDICARE AND
MEDICAID SERVICES,
7500 Security Boulevard
Baltimore, MD 21244;

ROBERT F. KENNEDY, JR., in his official
capacity as Secretary of the U.S. Department of
Health and Human Services,
200 Independence Avenue, S.W.
Washington, DC 20201;

MEHMET OZ, in his official capacity as
Administrator of the Centers for Medicare and
Medicaid Services,
7500 Security Boulevard
Baltimore, MD 21244,

Defendants.

No. _____

COMPLAINT

Plaintiff AbbVie Inc. brings this action for declaratory and injunctive relief against the Department of Health and Human Services (HHS), the Centers for Medicare & Medicaid Services (CMS), and the heads of those agencies in their official capacities, and alleges as follows:

PRELIMINARY STATEMENT

1. This lawsuit challenges CMS's decision to select BOTOX® for the prescription-drug price controls established by the Inflation Reduction Act of 2022 (IRA). *See* 42 U.S.C.

§ 1320f *et seq.* Through the IRA, Congress for the first time granted the federal government the authority to place price controls on certain medications covered under Medicare. In so doing, Congress expressly *excluded* certain categories of medications from eligibility in the price-control program. *See* 42 U.S.C. § 1320f-1(e)(3). Unlike previous challenges related to the IRA, this lawsuit is the first that arises from CMS’s violation of one of those express statutory exclusions established by Congress: namely, the IRA’s exclusion of “plasma-derived products” from price controls.

2. While commonly known for its cosmetic uses, BOTOX was first developed as a medicine. It is approved by the Food and Drug Administration (FDA) to treat multiple serious and debilitating diseases, including chronic migraine, urinary incontinence, eye-and-neck movement disorders, and many other non-cosmetic medical conditions. BOTOX is the only FDA-approved product to treat the serious eye disorders blepharospasm (*i.e.*, uncontrollable eye blinking) in adolescents and strabismus (*i.e.*, crossed eyes) in adults and adolescents. BOTOX works by selectively blocking nerve communications to targeted muscles and sensory neurons involved in pain transmission, enabling highly precise administration to selected areas of the body. That targeted approach minimizes unwanted side effects and enables more effective treatment, particularly for patients who have not responded to other therapies. Medicare coverage for BOTOX only extends to its medical uses, and it is BOTOX’s medical uses that are the subject of this litigation.

3. Since its first FDA approval in 1989, BOTOX has always consisted of just three ingredients: onabotulinumtoxinA (onabotA), human serum albumin (HSA), and sodium chloride. HSA is a protein extracted from human blood plasma. HSA makes up approximately one-third of BOTOX and plays a critical role in the safety and efficacy of the product.

4. Because HSA is sourced from donated human blood plasma, its supply is inherently constrained by donor supply and vulnerable to supply-chain interruptions. Natural variability among donors, as well as the chemical and physical processes required to isolate HSA from other plasma components, introduces additional variability that contributes to manufacturing challenges. Products that contain ingredients that come from human blood are also subject to strict regulatory requirements regarding their manufacturing and labeling. Such supply vulnerabilities and operational complexities are inherent to manufacturing plasma-derived products, as Congress implicitly acknowledged when it excluded plasma-derived products from IRA price controls.

5. BOTOX is a biological product derived from human blood plasma that should have been excluded from selection under the plain language of the IRA. Congress granted CMS authority to select a drug or biological product for price controls only if that drug or biological product meets certain conditions. Specifically, the product must satisfy the statutory definition of a “qualifying single source drug.” 42 U.S.C. § 1320f-1(d)(1). The IRA expressly provides that the phrase “qualifying single source drug” does not include “[p]lasma-derived products”—that is, a “biological product that is derived from human whole blood or plasma.” *Id.* § 1320f-1(e)(3)(C). BOTOX undoubtedly falls within that exclusion. Because HSA is sourced from plasma collected from human donors, BOTOX is a “plasma-derived product” that Congress excluded from the price-control program. In failing to apply this exclusion to BOTOX, CMS has exceeded its statutory authority under the IRA and thus violated the Administrative Procedure Act or, alternatively, acted *ultra vires*.

6. The plain text of the IRA’s plasma-derived-products exclusion suffices to set aside the selection of BOTOX. In addition, CMS’s actions will lead to the violation of AbbVie’s constitutional rights in several ways. By selecting BOTOX and imposing a “maximum fair price,”

CMS will (1) force AbbVie, under threat of ruinous tax liability or exclusion from federal government programs, to turn over physical doses of the product to Medicare beneficiaries at confiscatory prices without just compensation in violation of the Takings Clause; (2) require AbbVie to express an untrue statement that it has acceded to a “fair” price in violation of the First Amendment; and (3) subject AbbVie to a one-sided price-setting process lacking the hallmarks of due process. Those constitutional violations also independently entitle AbbVie to declaratory and injunctive relief.

THE PARTIES

7. Plaintiff AbbVie Inc. (AbbVie) is a corporation organized and existing under the laws of Delaware with its corporate headquarters at 1 North Waukegan Road, North Chicago, Illinois 60064. AbbVie Inc. holds the biologics license application (BLA) for BOTOX.¹

8. AbbVie is engaged in the discovery and delivery of innovative medicines and solutions that enhance people’s lives. AbbVie develops, sells, and distributes a broad range of pharmaceutical products, including the finished biological products that are marketed under the name BOTOX.

9. Defendant Department of Health and Human Services (HHS) is an executive department of the United States government headquartered in Washington, D.C. HHS is responsible for administering the Medicare program and the statutory provisions challenged here.

¹ The FDA’s drug database lists “Allergan” as the “Company” under the BLA for BOTOX. *See* U.S. Food & Drug Administration, [Drugs@FDA: FDA-Approved Drugs](https://tinyurl.com/FDADrugsAllergan), <<https://tinyurl.com/FDADrugsAllergan>>. But AbbVie is the actual BLA holder of BOTOX. AbbVie acquired Allergan, Inc., in 2020, and, as agency correspondence and product labels posted to the FDA’s drug database illustrate, AbbVie is the BLA holder of all BOTOX products.

10. Defendant Centers for Medicare & Medicaid Services (CMS) is an administrative agency within HHS that is headquartered in Baltimore, Maryland. It administers the Medicare program and the statutory provisions challenged here.

11. Defendant Robert F. Kennedy, Jr., is the Secretary of the Department of Health and Human Services. He oversees the Medicare program and is responsible for administering the statutory provisions challenged here. He is sued in his official capacity.

12. Defendant Mehmet Oz is the CMS Administrator. He administers the Medicare program and the statutory provisions challenged here on behalf of the Secretary of HHS. He is sued in his official capacity.

JURISDICTION AND VENUE

13. This Court has jurisdiction under 28 U.S.C. §§ 1331 and 1346 because this action arises under the laws of the United States, including the United States Constitution, and because an agency of the United States is a Defendant. Sovereign immunity is not an obstacle to this suit for injunctive and declaratory relief. *See* 5 U.S.C. § 702.

14. An actual controversy exists between the parties within the meaning of 28 U.S.C. § 2201(a), and this Court may grant declaratory relief, injunctive relief, and other appropriate relief pursuant to 28 U.S.C. §§ 2201-2202 and 5 U.S.C. §§ 703-706.

15. Venue is proper in this judicial district under 28 U.S.C. § 1391(e)(1) because this action is brought against officers and agencies of the United States and at least one defendant resides in this district.

BACKGROUND

I. Federal Healthcare Programs and Prescription Drugs

A. Medicare and Medicaid

16. The Medicare and Medicaid programs—two of the world’s largest health insurance programs, both operated by the federal government—provide health insurance to over 100 million eligible Americans.

17. Medicare offers prescription drug coverage through Medicare Part B, which covers, among other things, physician-administered drugs, and through Medicare Part D, which covers self-administered prescription drugs. In addition, every state currently provides coverage for out-patient prescription drugs to most enrollees within their state Medicaid programs.

18. The federal government faces practically no competition from private insurers in markets served by Medicare and Medicaid. The two programs account for nearly 40% of the broader domestic health-care market.

19. Federal agencies have generally imposed an “all in” or “all out” requirement for these federal health care programs, forcing manufacturers either to participate in Medicare and Medicaid or to withdraw all of their products from those programs. Because Medicare and Medicaid dominate the health care market, withdrawing all of a manufacturer’s products from these federal health care programs is not a viable option.

B. The Drug Price Negotiation Program

20. In 2022, Congress enacted the IRA, which included a directive to create the Drug Price Negotiation Program (Program). In so doing, Congress delegated authority to CMS to “negotiate” prices on certain drug and biological products pursuant to statutory requirements. *See* 42 U.S.C. § 1320f(a).

21. The IRA directs CMS to select a set number of drugs each year to subject to the Program. The number of drugs selected for the Program is cumulative: for initial price applicability year (IPAY) 2026, CMS selected 10 new drugs; for each of IPAY 2027 and IPAY 2028, the agency selected 15 new drugs; and for all future IPAYs, CMS must choose 20 new drugs each year. *See* 42 U.S.C. §§ 1320f(d), 1320f-1(a)(1)-(4). Given that cumulative selection process, projections show that, within ten years, half of all Medicare drug spending will be controlled by the IRA’s new price-setting process under the Program.

22. The selected drugs are chosen out of a pool of “negotiation-eligible” drugs, which are then ranked based on “total expenditures” under Medicare over the previous 12-month period. 42 U.S.C. § 1320f-1(b)(1)-(2). To be “negotiation-eligible”—and thus subject to selection under the Program—a drug must be a “qualifying single source drug.” 42 U.S.C. § 1320f-1(d), (e).

23. The term “qualifying single source drug” includes (1) drug products “approved” and “marketed” under a new drug application, that have been licensed for at least seven years, and that are not the listed drug for a marketed generic drug; and (2) biological products “licensed” and “marketed” under a BLA, that have been licensed for at least 11 years, and that are not the reference product for a marketed biosimilar product. 42 U.S.C. § 1320f-1(e)(1)(A), (B).

24. Congress excluded from the Program certain categories of drugs or biological products that would otherwise meet the definition of a “qualifying single source drug.” 42 U.S.C. § 1320f-1(e)(3). As relevant here, the IRA limits CMS’s authority to select drugs for the Program by specifying that “the term ‘qualifying single source’ drug does not include . . . [p]lasma-derived products,” defined as “[a] biological product that is derived from human whole blood or plasma.” 42 U.S.C. § 1320f-1(e)(3)(C).

25. In its final implementation guidance for IPAY 2028, CMS stated that, “[f]or purposes of this exclusion, a plasma-derived product is a licensed biological product that is derived from human whole blood or plasma, as indicated on the approved product labeling.” Centers for Medicare & Medicaid Services, Medicare Drug Price Negotiation Program: Final Guidance, Implementation of Sections 1191 – 1198 of the Social Security Act for Initial Price Applicability Year 2028 and Manufacturer Effectuation of the Maximum Fair Price in 2026, 2027, and 2028, at 173 (Sept. 30, 2025) (IPAY 2028 Final Guidance). The guidance also states that CMS will refer to “product information available on the FDA Approved Blood Products website” and “databases such as FDALabel and the FDA Online Label Repository” to “identify plasma-derived products” for purposes of the plasma-derived-products exclusion. *Id.* at 27 (footnotes omitted); *accord id.* at 173. The guidance further provides that “CMS also will consult with FDA, as appropriate.” *Id.* at 173.

26. Only if a drug or biological product meets the definition of a qualifying single source drug—and does not fall into one of the exclusions to that definition that Congress created—does CMS have the authority to select the product for the Program.

C. Consequences of Selection for the Program

27. For manufacturers of selected products, the consequences of selection are immediate. Once CMS publishes the list of selected drugs, the affected manufacturers have approximately one month to “enter into agreements” with CMS, under which they must agree to “negotiate to determine . . . a maximum fair price,” submit “information that [CMS] requires to carry out the negotiation,” and “compl[y] with requirements” that CMS determines “to be necessary for purposes of administering the program and monitoring compliance with the program.” 42 U.S.C. § 1320f-2(a).

28. CMS released template manufacturer agreements that require manufacturers to express that the “manufacturer agree[s]” that it will “negotiate to determine . . . a maximum fair price,” and that once “the manufacturer and CMS have engaged in negotiation of the price,” that price will be “binding” upon the manufacturer. Medicare Drug Price Negotiation Program Agreement 1-2, 7-8, <<https://tinyurl.com/ManufacturerAgreementTemplate>> (Template Agreement). The Template Agreement contains a disclaimer: “Use of the term ‘maximum fair price’ and other statutory terms throughout this Agreement reflects the parties’ intention that such terms be given the meaning specified in the statute and does not reflect any party’s views regarding the colloquial meaning of those terms.” *Id.* at 4.

29. If a manufacturer refuses to sign CMS’s agreement to “negotiate,” the manufacturer must pay an escalating daily excise tax that starts at 186% and increases to 1,900% of the drug’s daily sales. 26 U.S.C. § 5000D; *see* Molly F. Sherlock et al., Congressional Research Service, R47202, Tax Provisions in the Inflation Reduction Act of 2022 (H.R. 5376), at 4 (Aug. 10, 2022). A manufacturer that does not agree to “negotiate” may avoid this excise tax only by withdrawing *all* of its products from Medicare and Medicaid. IPAY 2028 Final Guidance 257-259 & n.148.

30. As part of entering into an agreement with CMS to negotiate a “maximum fair price,” a manufacturer must promise to “provide access to such price” for the “selected drug” to eligible individuals and entities. 42 U.S.C. § 1320f-2(a)(1). Failure to do so will trigger civil monetary penalties of ten times the difference between the price the manufacturer actually charges and the mandated price. 42 U.S.C. § 1320f-6(a). In addition, a manufacturer that violates the terms of its agreement with CMS will be subject to a statutorily specified civil monetary penalty of \$1 million per day. *See* 42 U.S.C. § 1320f-6(c).

31. During the price-setting process, CMS “shall . . . aim[] to achieve the lowest maximum fair price for each selected drug,” 42 U.S.C. § 1320f-3(b)(1), and in no case may agree to a price exceeding the ceiling established by statute, *see* 42 U.S.C. § 1320f-3(b)(2)(F)(i). For a drug that has been on the market for at least 16 years, that price ceiling may be no more than 40% of the wholesale price for the drug in the private market. For a drug that has been on the market for at least 16 years, that price ceiling may be no more than 40% of the wholesale price for the drug in the private market. 42 U.S.C. § 1320f-3(c)(3)(C). For drugs that have been on the market for between 12 and 16 years or for less than 12 years, that price ceiling may be no more than 65% and 75%, respectively, of the private market wholesale price. 42 U.S.C. § 1320f-3(c)(3)(A), (B). CMS has often set prices that are discounted at least 50% from the list price and has imposed discounts as high as 85% off of the list price. *See* Centers for Medicare & Medicaid Services, Medicare Drug Price Negotiation Program: Negotiated Prices for Initial Price Applicability Year 2026, at 2 (2024); Centers for Medicare & Medicaid Services, Medicare Drug Price Negotiation Program: Negotiated Prices for Initial Price Applicability Year 2027, at 2 (2025). For drugs that have been on the market at least 16 years, CMS has imposed an average reduction of more than 70% off the list price. *Id.*

32. “[T]here is no limit to how low HHS’s offer can be.” *National Infusion Center Association v. Becerra*, 116 F.4th 488, 495 (5th Cir. 2024). And “[i]f the manufacturer fails to reach an agreement” on a “maximum fair price” or “walk[s] away from negotiations,” the penalties described above will apply. *Id.* (internal quotation marks omitted).

33. Once a manufacturer enters an agreement with HHS to sell at the dictated price, sales must continue at that price until a specified time after a generic or biosimilar version of the

drug is approved and marketed, *see* 42 U.S.C. § 1320f-1(c)(1), or the drug is picked for “renegotiation,” *see* 42 U.S.C. § 1320f-3(f).

34. The IRA bars both administrative and judicial review of various aspects of the drug-selection and price-setting process. *See* 42 U.S.C. § 1320f-7.

II. BOTOX

A. BOTOX Is An Innovative Biological Product

35. BOTOX is a biological product that was first approved by the FDA in 1989.² Although widely known for its cosmetic uses such as reducing wrinkles, BOTOX has received 12 FDA approvals to treat serious medical conditions. This case focuses on BOTOX’s medical uses, which are reimbursed by Medicare and Medicaid and thus are implicated by its improper selection for governmental price-setting.

36. BOTOX’s first FDA approval was for the treatment of strabismus and blepharospasm, serious eye disorders caused by muscle dysfunction that substantially impact daily functioning, quality of life, and work productivity. Prior to BOTOX’s approval, the only available medications were generally ineffective and not FDA-approved for these uses; some also caused intolerable side effects. Alan B. Scott et al., *Treatment of Strabismus and Blepharospasm with Botox (onabotulinumtoxinA): Development, Insights, and Impact*, 102 *Medicine* S23, S24 (2023). These conditions were thus often treated with eye muscle surgeries, but the surgeries were often unsuccessful or resulted in complications. *Id.* BOTOX, which allows for the targeted dosing of specific muscles, was developed to provide a less invasive, well-tolerated pharmacological

² The product known today as BOTOX was initially licensed by the FDA in 1989 under the name Oculinum. In 1991, Allergan acquired Oculinum and renamed it BOTOX a year later.

alternative. *Id.* at S24, S26. It was found to be an effective alternative to surgery and significantly reduced the risk of intolerable side effects linked to oral medicines. *Id.*

37. Since the initial approval of BOTOX, research and development efforts have resulted in this innovative therapy being used to address other severe, difficult-to-treat medical conditions. Today, BOTOX has 12 U.S. FDA approvals across 8 neurological diseases spanning both adult and pediatric populations. These are summarized in the table below:

BOTOX Indications	Approval Date	Description	
Blepharospasm	1989	Involuntary, repeated blinking, or spasm of eyelid muscles resulting in uncontrollable blinking or eyelid closure	
Strabismus	1989	Eye misalignment due to poor control of eye muscles resulting in double vision, reduced depth perception, eye strain, and potential vision loss	
Cervical dystonia	2000	Painful neurological condition due to involuntary neck muscle contractions, causing the head to twist, turn, or tilt uncontrollably in various directions	
Hyperhidrosis	2004	Skin disorder resulting in excessive sweating due to overactive sweat glands	
Spasticity*	2010	Adult Upper Limb	Debilitating neurological condition causing muscle stiffness and impaired movement that can interfere with movement and function, often seen after stroke, spinal cord injury, multiple sclerosis, traumatic brain injury, or cerebral palsy
	2016	Adult Lower Limb	
	2019	Pediatric Upper Limb	
	2019	Pediatric Lower Limb	
Chronic migraine	2010	Headaches on 15 or more days per month, often severely impacting daily life due to pain and other symptoms	
Neurogenic detrusor overactivity*	2011	Adult	Uncontrolled contraction of bladder muscles causing frequent, urgent urination or leakage, resulting from nerve damage from neurological conditions (e.g., spinal cord injury, multiple sclerosis)
	2021	Pediatric	
Overactive bladder	2013	Uncontrolled contraction of bladder muscles causing frequent, urgent urination or leakage, without underlying neurological cause or infection	

* = FDA approvals granted separately for different muscle groups and patient populations, each requiring additional clinical data to address variations in muscle type and injection methods, as well as differences in muscle size, function, treatment goals, and risk profiles.

38. While BOTOX was being used to treat overactive facial muscles, researchers discovered that BOTOX also decreased skin wrinkles at the site of injection. The FDA has since approved BOTOX—under the brand name BOTOX Cosmetic—for 4 cosmetic indications, including the smoothing of facial wrinkles in adults. BOTOX’s cosmetic uses are not covered by Medicare and Medicaid and are not subject to government price controls.

39. BOTOX’s broad range of medical uses are driven by its precise, targeted mechanism of action and strong safety profile, providing opportunities for continued innovation. In recent years, AbbVie has investigated new uses for BOTOX for additional severe and difficult-to-treat medical conditions. AbbVie has made—and continues to make—significant investments to advance toxin innovation, including discovering new uses and optimizing manufacturing processes. For example, AbbVie recently completed a \$69 million expansion of its domestic toxins research and development capabilities to more effectively manage the scientific challenges, high security, and regulatory demands of an innovative toxins portfolio.

B. BOTOX Supply Depends On HSA

40. Since its original approval, BOTOX has always consisted of three ingredients: onabotulinumtoxinA (onabotA), human serum albumin (HSA), and sodium chloride. OnabotA is a natural, biological protein produced from *clostridium botulinum* bacteria. HSA is a protein present in human blood plasma and sourced from human blood donors. Sodium chloride, commonly known as salt, is included in BOTOX to produce an isotonic solution that is in balance with body fluids.

41. BOTOX is not made up of all three ingredients in equal proportion or volume. The product contains approximately 100,000 times more HSA than onabotA. This is roughly equivalent to onabotA occupying a single seat in the University of Michigan’s football stadium—the

biggest stadium in the United States—while HSA occupies every other seat in the stadium. That has been the case since BOTOX launched in 1989.

42. BOTOX is licensed and marketed under a biologics license application (BLA 103000) held by AbbVie in three strengths. FDA has only ever licensed BOTOX in its finished dosage forms, which have always included HSA, and AbbVie’s ability to market BOTOX under this license depends on the presence of HSA. *See* 21 C.F.R. § 601.12 (setting forth FDA regulations governing changes to already-approved or licensed drug products).

43. The HSA in BOTOX is sourced from human plasma. The FDA-approved product labeling for BOTOX expressly states that the “product contains albumin, a derivative of human blood.” United States BOTOX Prescribing Information § 5.14 (2023) (BOTOX Prescribing Information) (Exhibit 1).

44. Because plasma-derived products like BOTOX rely on human donations, these products are particularly vulnerable to variability in plasma donation supply. Plasma-derived products also pose unique manufacturing challenges. Plasma fractionation is a multi-step process that separates and purifies specific proteins (such as HSA) from human plasma. Slight variations in fractionation processes can alter the properties of HSA and other plasma proteins in ways that can affect products that contain these proteins. These manufacturing challenges result in heightened risk of shortage. To try to protect against these risks to BOTOX supply, AbbVie has qualified two different HSA suppliers.

45. Even minor changes in either of these supplier’s HSA extraction processes or handling protocols can result in significant, costly changes to AbbVie’s BOTOX manufacturing process to maintain product consistency. BOTOX manufacturing process changes take years to develop and require FDA pre-approval before implementation. *See* 21 U.S.C. § 356a; 21 C.F.R.

§ 601.12(b). As a plasma-derived product, BOTOX supply is vulnerable to precisely the manufacturing and regulatory risks that led Congress to exclude plasma-derived products from the IRA.

C. HSA Plays A Critical Role In BOTOX

46. HSA is a necessary, integral ingredient in achieving BOTOX's therapeutic effects. Specifically, and in addition to constituting approximately one-third of the volume of BOTOX, HSA plays a critical function in managing the activity of onabotA, and it directly contributes to the safety and efficacy of BOTOX.

47. The FDA-approved formulation for BOTOX has always (and continues) to include HSA. AbbVie initially formulated BOTOX with HSA to protect onabotA, an extremely potent and complex molecule, from environmental factors that can affect the quality, stability, and performance of BOTOX. For example, HSA minimizes protein aggregation (or "clumping") that would reduce the activity of onabotA or trigger unwanted immune responses. HSA also limits protein loss via adsorption, which occurs when the protein sticks to surfaces or syringes; adsorption can contribute to inconsistency in the delivered dose. Moreover, HSA protects against toxin oxidation (*i.e.*, the breakdown of onabotA into other compounds), which is particularly important given the minute quantities of onabotA present in each BOTOX dose.

48. In the years since BOTOX's approval, the scientific community's understanding of the relationship between HSA and toxins has further expanded. Over the last two decades, peer-reviewed studies have reported that the concentration of HSA affects the activity of toxins and enables the effective administration of lower dosages of toxin products. *See, e.g.,* Anna Kutschenko et al., *The Role of Human Serum Albumin and Neurotoxin Associated Proteins in the Formulation of BoNT/A products*, 168 *Toxicon* 158, 161 (2019); Jens D. Rollnik et al., *Low-Dose*

Treatment of Cervical Dystonia, Blepharospasm and Facial Hemispasm with Albumin-Diluted Botulinum Toxin Type A under EMG Guidance, 43 *European Neurology* 9, 11 (2000).

49. Building on those observations and using modern analytical tools, AbbVie recently conducted additional studies regarding how HSA impacts onabotA and the efficacy of BOTOX. AbbVie observed that HSA's presence leads to greater binding between onabotA and the targeted nerve cell receptors, resulting in greater toxin peak effect and duration. AbbVie's studies also demonstrated that, in the presence of HSA, onabotA remains longer near the injection site, increasing receptor binding. Overall, AbbVie's findings clarify HSA's significance in BOTOX and demonstrate that HSA directly contributes to the therapeutic effects of BOTOX. This has always been true—BOTOX's formulation has not changed since its original licensure. If HSA were removed from BOTOX, it would be a different product that would require new data to secure FDA approval.

D. BOTOX Is Selected For The Drug Price Negotiation Program

50. In 2025, AbbVie's internal projections suggested that, if not for the IRA's express exclusion for plasma-derived products, CMS might select BOTOX for the Program based on its methodology for calculating Medicare Part B and D expenditures.

51. To the best of AbbVie's knowledge, CMS has never applied the plasma-derived exclusion. Accordingly, AbbVie sought to engage with CMS regarding BOTOX's exemption from the Program as a plasma-derived product. AbbVie sent CMS multiple emails and letters, and AbbVie personnel met with CMS representatives on several occasions. In these communications and meetings, AbbVie explained that the plasma-derived exclusion precluded CMS from selecting BOTOX for the Program. CMS never refuted AbbVie's view. And despite these multiple letters

and meetings, CMS provided no feedback with respect to the application of the plasma-derived exclusion.

52. On January 27, 2026, CMS selected BOTOX and BOTOX Cosmetic for IPAY 2028 of the Program. CMS provided no explanation for its failure to apply the statute’s plasma-derived exception to BOTOX.

CLAIMS FOR RELIEF

COUNT I

(Challenge to CMS’s Actions: Violation of the Administrative Procedure Act— Action in Excess of Statutory Authority)

53. AbbVie realleges and incorporates by reference all prior and subsequent paragraphs.

54. The Administrative Procedure Act provides that a “reviewing court shall . . . hold unlawful and set aside agency action . . . found to be . . . in excess of statutory jurisdiction, authority, or limitations, or short of statutory right.” 5 U.S.C. § 706(2)(C).

55. By selecting BOTOX for the Program, CMS acted in excess of its statutory authority. Through the IRA’s specific eligibility requirements, Congress expressly limited CMS’s authority to select drugs and biological products for inclusion in the Program. As relevant here, only a “qualifying single source drug” may qualify as a “negotiation-eligible drug” subject to selection under the Program. 42 U.S.C. § 1320f-1(d)(1).

56. In the IRA, Congress expressly provides that “the term ‘qualifying single source drug’ does not include” certain excluded products. 42 U.S.C. § 1320f-1(e)(3). One such exclusion is for a “plasma-derived product[,]” which the IRA defines as a “biological product that is derived from human whole blood or plasma.” 42 U.S.C. § 1320f-1(e)(3)(C).

57. That straightforward language makes clear that the plasma-derived-products exclusion applies when a biological product is “derived from”—*i.e.*, “obtain[ed]” from—“human whole blood or plasma.” *See* The New Oxford Dictionary of English 498 (2001).

58. BOTOX undoubtedly satisfies the exclusion’s requirement because one of its components, HSA, is sourced from plasma collected from human donors.

59. FDA licensed BOTOX in its finished dosage forms, which include HSA, and BOTOX’s approved product labeling confirms that it contains “albumin, a derivative of human blood.” BOTOX Prescribing Information § 5; *see id.* § 11. BOTOX thus falls under the exclusion’s plain text based on its composition and labeling.

60. Because BOTOX satisfies the plasma-derived-products exclusion, CMS has no authority under the IRA to select BOTOX. CMS’s decision to select BOTOX thus violates the express statutory mandate of the IRA.

61. The IRA’s judicial-review bar does not apply to AbbVie’s APA claim. The IRA precludes judicial review of “the determination of qualifying single source drugs under section 1320f–1(e) of this title.” 42 U.S.C. § 1320f-7(2). But the IRA states that a “qualifying single source drug” does not include “[p]lasma-derived products” such as BOTOX. 42 U.S.C. § 1320f-1(e)(3). Under well-established circuit precedent, a “jurisdiction-stripping provision does not apply if the agency’s action fails to qualify as the kind of action for which review is barred.” *American Hospital Association v. Azar*, 964 F.3d 1230, 1238 (D.C. Cir. 2020). Consideration of the IRA’s judicial-review bar thus “merges” with “the legality of [agency] action,” and this Court thus may adjudicate this claim. *Id.*

62. CMS’s selection of BOTOX for price setting constitutes final agency action for which AbbVie has no other adequate remedy under 5 U.S.C. § 704.

COUNT II

(Challenge to CMS's Actions: Ultra Vires and Unlawful Conduct)

63. AbbVie realleges and incorporates by reference all of the allegations contained in the preceding paragraphs of this complaint as though set forth fully herein.

64. “Administrative agencies are creatures of statute,” and they “possess only the authority that Congress has provided.” *NFIB v. Department of Labor*, 595 U.S. 109, 117 (2022). “Judicial review for *ultra vires* agency action rests on the longstanding principle that if an agency action is unauthorized by the statute under which [the agency] assumes to act, the agency has violated the law and the courts generally have jurisdiction to grant relief.” *Federal Express Corp. v. Department of Commerce*, 39 F.4th 756, 763 (D.C. Cir. 2022) (internal quotation marks and citation omitted).

65. Courts have identified *ultra vires* action when an agency attempts to exercise “power that had been specifically withheld” in a “specific prohibition” of a statute. *Leedom v. Kyne*, 358 U.S. 184, 188-189 (1958). An agency also acts *ultra vires* when it “ignore[s] [a] limitation” in a statute and “totally pervert[s] the meaning of the statute.” *Aid Association for Lutherans v. USPS*, 321 F.3d 1166, 1175 (D.C. Cir. 2003). And an agency acts *ultra vires* when it “choose[s] to ignore” “Congress’s directives”; “fails to meet its statutory obligation”; or adopts a statutory “construction [that] requires adding text to the Act that Congress pointedly omitted.” *National Association of Postal Supervisors v. USPS*, 26 F.4th 960, 974, 977 (D.C. Cir. 2022).

66. This Court retains jurisdiction to set aside CMS’s selection of BOTOX as *ultra vires* action. *See Leedom*, 358 U.S. at 185. Such “nonstatutory review [is] available” because, as explained above, the selection of BOTOX is “an attempted exercise of power that had been

specifically withheld” under a “specific prohibition” in the IRA—namely, the plasma-derived-products exclusion. *Nuclear Regulatory Commission v. Texas*, 605 U.S. 665, 681 (2025) (quoting *Leedom*, 358 U.S. at 188-189)).

67. Accordingly, if this Court does not set aside CMS’s selection of BOTOX as unlawful under the APA, it should do so on the alternative basis that the agency’s action was *ultra vires*. See *Chamber of Commerce v. Reich*, 74 F.3d 1322, 1327 (D.C. Cir. 1996) (noting that, even when “a plaintiff is unable to bring his case predicated on either a specific or a general statutory review provision, he may still be able to institute a non-statutory review action”).

COUNT III

(Challenge to CMS’s Actions: Violation of the Fifth Amendment—Categorical Taking)

68. AbbVie realleges and incorporates by reference all of the allegations contained in the preceding paragraphs of this complaint as though set forth fully herein.

69. The Fifth Amendment prohibits the government from taking “private property . . . for public use, without just compensation.”

70. CMS has violated the Fifth Amendment by forcing AbbVie to turn over physical doses of BOTOX to Medicare beneficiaries at confiscatory prices set by CMS without paying just compensation. See *Horne v. Department of Agriculture*, 576 U.S. 350, 360-363 (2015).

71. CMS is in the process of taking AbbVie’s personal property by requiring the company, under threat of devastating penalties or total withdrawal of all of its drugs from Medicare and Medicaid, to sign an agreement to hand over its BOTOX products at a confiscatory price to which AbbVie would never voluntarily agree. The IRA’s threat of crippling penalties is a “sword of Damocles” hanging over AbbVie’s head, compelling it to participate in the Program and turn

over its BOTOX products to Medicare beneficiaries at prices dictated by CMS. *Bristol Myers Squibb Co. v. Secretary*, 155 F.4th 245, 273 (3d Cir. 2025) (Hardiman, J., dissenting).

72. The “maximum fair price” that CMS will impose—which will almost certainly be lower than the statutory ceiling price—will be both arbitrary and confiscatory and impermissibly below the threshold for just compensation set by the Constitution.

73. CMS has thus taken AbbVie’s property without providing the just and adequate compensation required by the Fifth Amendment.

74. Even supposing that AbbVie could avoid this taking by removing all of its products from Medicare and Medicaid—something that is not a viable option for multiple reasons already discussed—the selection of BOTOX is nevertheless unconstitutional because it impermissibly conditions AbbVie’s ability to participate in those programs on the surrendering of its constitutional rights. *See Koontz v. St. Johns River Water Management District*, 570 U.S. 595, 606 (2013). Conditioning benefits on the relinquishment of constitutional rights runs afoul of the unconstitutional-conditions doctrine, which applies even if “a person has no ‘right’ to a valuable governmental benefit and even though the government may deny him the benefit for any number of reasons.” *Perry v. Sindermann*, 408 U.S. 593, 597 (1972).

75. AbbVie seeks declaratory relief with respect to its Takings Clause claim. Such relief is appropriate for two reasons.

76. *First*, a damages suit would be “utterly pointless.” *Eastern Enterprises v. Apfel*, 524 U.S. 498, 521 (1998) (plurality opinion) (internal quotation marks and citation omitted). AbbVie would need to bring a suit regarding each instance of a taking of a BOTOX product. “Congress could not have contemplated” that “[e]very dollar [saved] pursuant to [the IRA] would

be presumed to generate a dollar of . . . compensation.” *Id.* (internal quotation marks and citation omitted).

77. *Second*, declaratory relief for a Takings Clause claim is appropriate when a statute does not provide “advance assurance of adequate compensation in the event of a taking.” *Duke Power Co. v. Carolina Environmental Study Group, Inc.*, 438 U.S. 59, 71 n.15 (1978). Here, the IRA does not provide any such assurances.

COUNT IV

(Challenge to CMS’s Actions: Violation of the First Amendment—Free Speech)

78. AbbVie realleges and incorporates by reference the foregoing paragraphs as though set forth fully herein.

79. The First Amendment protects against laws “abridging the freedom of speech.”

80. Freedom of speech “includes both the right to speak freely and the right to refrain from speaking at all.” *Wooley v. Maynard*, 430 U.S. 705, 714 (1977).

81. The First Amendment does not permit laws that “[c]ompel[] individuals to mouth support for views they find objectionable.” *Janus v. American Federation of State, County, and Municipal Employees, Council 31*, 585 U.S. 878, 892 (2018).

82. As the IRA’s text provides, AbbVie must express in a contract that it has “agreed” to receive a “maximum fair price” for BOTOX. 42 U.S.C. § 1320f-2(a). AbbVie must accede to these statements *before* the so-called negotiation has begun. *See* 42 U.S.C. § 1320f-2(a)(1). “[W]hen a deprivation of First Amendment rights is at stake, a plaintiff need not wait for the damage to occur before filing suit.” *Mahmoud v. Taylor*, 606 U.S. 522, 560-561 (2025) (citing *Susan B. Anthony List v. Driehaus*, 573 U.S. 149, 158 (2014)).

83. Moreover, as CMS’s template manufacturer agreement illustrates, AbbVie will be forced to state that it “agree[s]” to “negotiate to determine . . . a maximum fair price” and that the resulting price was “[n]egotiated,” “fair,” and something to which AbbVie “agree[s].” Template Agreement at 2, 7.

84. AbbVie strongly disagrees with those statements but will be forced to make them anyway. Specifically, AbbVie does not believe that any price achieved through the Program would be the result of a negotiation or voluntary agreement—let alone that the final price would be “fair,” given the government’s ability to pick the price unilaterally. But AbbVie has no choice in whether to participate in the Program because it would face potentially catastrophic economic consequences if it declined to do so. AbbVie will thus be converted into a “vehicle for spreading a message with which it disagrees.” *Pacific Gas & Electric Co. v. Public Utilities Commission*, 475 U.S. 1, 17 (1986) (plurality opinion); see *Bristol Myers Squibb*, 155 F.4th at 284-286 (Hardiman, J., dissenting).

85. To the extent CMS seeks to include a disclaimer in AbbVie’s agreement, it would not cure any First Amendment violation. That is because a disclaimer would not eliminate the pressure on AbbVie to express statements with which it disagrees and would not otherwise make. See *Pacific Gas & Electric*, 475 U.S. at 15 n.11 (plurality opinion). The taint of compelled speech still leaves its mark when the government “require[s] speakers to affirm in one breath that which they deny in the next.” *Id.* at 16.

86. The government has no compelling or important interest in forcing AbbVie to speak these untruths about the purportedly “negotiated” price of BOTOX. The most that can be said for the IRA’s regime is that the government has an interest in convincing the public that the IRA brings the government and manufacturers together in good faith for a fair negotiation. But that is

not the reality; rather, at the risk of catastrophic economic consequences, manufacturers are forced to the table to accept the government's non-negotiable negotiation offer.

87. An injunction is necessary because manufacturers would suffer irreparable harm to their constitutional rights if forced to submit to the Program. *See, e.g., eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 391 (2006); *Elrod v. Burns*, 427 U.S. 347, 373 (1976) (plurality opinion). Moreover, the equities and public interest favor injunctive relief, because the government has no meaningful justification for maintaining the IRA's unconstitutional faux-negotiation scheme. *See Kareem v. Trump*, 960 F.3d 656, 668 (D.C. Cir. 2020).

88. The Court should thus declare unconstitutional the IRA's requirement that manufacturers "agree" to "maximum fair prices." 42 U.S.C. § 1320f-2(a). The Court should enjoin CMS from forcing AbbVie to sign a "[m]anufacturer agreement[]" or "agree to" a "maximum fair price." *Id.* Further, to the extent AbbVie is forced to sign such a "[m]anufacturer agreement[]" during the pendency of this lawsuit, the Court should declare any such agreement null and void.

COUNT V

(Challenge to CMS's Actions: Violation of the Fifth Amendment—Due Process)

89. AbbVie realleges and incorporates by reference the foregoing paragraphs as though set forth fully herein.

90. The Fifth Amendment provides that "[n]o person shall be deprived of life, liberty, or property, without due process of law."

91. Under the Fifth Amendment's Due Process Clause, the government may not deprive a person of property without first following constitutionally sufficient procedures. *See Kentucky Department of Corrections v. Thompson*, 490 U.S. 454, 460 (1989). Those procedures

include notice and an opportunity to be heard “at a meaningful time and in a meaningful manner,” *Armstrong v. Manzo*, 380 U.S. 545, 552 (1965); *see also Mathews v. Eldridge*, 424 U.S. 319, 333 (1976), as well as other protections that work to prevent, to the extent possible, an erroneous deprivation of property, *see Gilbert v. Homar*, 520 U.S. 924, 930-932 (1997).

92. In imposing a “maximum fair price” on BOTOX, CMS will not follow constitutionally sufficient procedures. CMS’s negotiation process is arbitrary and does not comply with basic requirements of due process. CMS has not created any forum in which AbbVie may be heard and may lodge any objections, including objections related to the plasma-derived-products exclusion. As this case illustrates, moreover, CMS is not required under the IRA to provide an explanation, much less a reasoned explanation, for why it has selected a drug to be subject to the Program in the first place. Those concerns are aggravated by the fact that CMS’s actions are largely insulated from judicial and administrative review.

93. Further, CMS will act as both the arbiter of the “negotiated” price and a party with a pecuniary interest in that price being as low as possible. This conflict of interest and the lack of a neutral arbiter violate longstanding due-process precedents.

94. AbbVie has multiple property interests related to BOTOX that are intruded upon by CMS’s unlawful actions, including its interests in physical BOTOX doses; the regulatory exclusivities and patents covering BOTOX and related intellectual property rights; the loss of the expected market value AbbVie invested in BOTOX; and the confidential and proprietary data AbbVie will be forced to provide to CMS.

95. AbbVie has a constitutionally protected property interest in its BOTOX products and substantial investment-backed expectations to be free from price controls that are “arbitrary, discriminatory, or demonstrably irrelevant to the policy the legislature is free to adopt.” *In re*

Permian Basin Area Rate Cases, 390 U.S. 747, 769-770 (1968) (quoting *Nebbia v. New York*, 291 U.S. 502, 539 (1934)). As has been the experience with other manufacturers under the Program, CMS’s price controls, coupled with its faux-negotiation regime, will take away AbbVie’s property interests, without affording it a meaningful opportunity to be heard before suffering significant economic losses.

PRAYER FOR RELIEF

Wherefore AbbVie prays for the following relief:

- A. Declare that CMS has violated the Administrative Procedure Act (or, alternatively, acted *ultra vires*) by exceeding the limitations on its statutory authority set forth in the Inflation Reduction Act of 2022;
- B. Vacate and set aside CMS’s selection of BOTOX under the Administrative Procedure Act (or, alternatively, as an *ultra vires* action);
- C. Declare that CMS has violated the Fifth Amendment by physically taking AbbVie’s property without providing just and adequate compensation;
- D. Declare that CMS has violated the First Amendment by compelling AbbVie to express agreement that it is receiving a “fair price” for BOTOX products under the IRA’s price-negotiation program;
- E. Declare that CMS’s selection of BOTOX violates the Due Process Clause of the Constitution’s Fifth Amendment;
- F. Enter a permanent injunction enjoining CMS from applying the drug-pricing provisions of the IRA to BOTOX, including in any administrative proceeding;
- G. Award AbbVie reasonable attorneys’ fees and costs, plus interest accruing thereon, under 28 U.S.C. § 2412; and

H. Grant such other and further relief as the Court may deem appropriate.

Dated: February 11, 2026
Washington, DC

PAUL, WEISS, RIFKIND,
WHARTON &
GARRISON LLP

By: /s/ Kannon K. Shanmugam
Kannon K. Shanmugam

Kannon K. Shanmugam (D.C. Bar No. 474304)
James Durling (D.C. Bar No. 1617226)*
Eleanor K. Ritter (D.C. Bar No. 90041795)*
2001 K Street, N.W.
Washington, DC 20006
(202) 223-7300
kshanmugam@paulweiss.com

S. Conrad Scott (D.C. Bar No. 1685829)*
Joshua A. Altman*
1285 Avenue of the Americas
New York, NY 10019
(212) 373-3000

**Pro hac vice* applications forthcoming

Attorneys for Plaintiff AbbVie Inc.

EXHIBIT 1

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BOTOX® safely and effectively. See full prescribing information for BOTOX.

BOTOX® (onabotulinumtoxinA) for injection, for intramuscular, intradetrusor, or intradermal use

Initial U.S. Approval: 1989

WARNING: DISTANT SPREAD OF TOXIN EFFECT

See full prescribing information for complete boxed warning.

The effects of BOTOX 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 an underlying condition that would predispose them to these symptoms. (5.1)

INDICATIONS AND USAGE

BOTOX is an acetylcholine release inhibitor and a neuromuscular blocking agent indicated for:

- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition [e.g., spinal cord injury (SCI), multiple sclerosis (MS)] in adults who have an inadequate response to or are intolerant of an anticholinergic medication (1.1)
- Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication. (1.2)
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer) (1.3)
- Treatment of spasticity in patients 2 years of age and older (1.4)
- Treatment of cervical dystonia in adult patients, to reduce the severity of abnormal head position and neck pain (1.5)
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients (1.6)
- Treatment of blepharospasm associated with dystonia in patients 12 years of age and older (1.7)
- Treatment of strabismus in patients 12 years of age and older (1.7)

Limitations of Use

Safety and effectiveness of BOTOX have not been established for:

- Prophylaxis of episodic migraine (14 headache days or fewer per month) (1.3)
- Treatment of hyperhidrosis in body areas other than axillary (1.6)

DOSAGE AND ADMINISTRATION

- Follow indication-specific dosage and administration recommendations. In a 3 month interval, do not exceed a total dose of:
 - Adults: 400 Units
 - Pediatrics: the lesser of 10 Units/kg or 340 Units (2.1)
- See Preparation and Dilution Technique for instructions on BOTOX reconstitution, storage, and preparation before injection (2.2)
- Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor (2.3)
- Adult Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor (2.3)
- Pediatric Detrusor Overactivity associated with a Neurologic Condition: 0.5 mL injections across 20 sites into the detrusor (2.4)
 - Greater than or equal to 34 kg: Recommended total dose is 200 Units
 - Less than 34 kg: Recommended total dose is 6 Units/kg
- Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles (2.5)
- Adult Upper Limb Spasticity: Recommended total dose up to 400 Units divided among affected muscles (2.6)
- Adult Lower Limb Spasticity: Recommended total dose 300 Units to 400 Units divided across ankle and toe muscles (2.6)
- Pediatric Upper Limb Spasticity: Recommended total dose 3 Units/kg to 6 Units/kg (maximum 200 Units) divided among affected muscles (2.7)

- Pediatric Lower Limb Spasticity: Recommended total dose 4 Units/kg to 8 Units/kg (maximum 300 Units) divided among affected muscles (2.7)
- Cervical Dystonia: Base dosing on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history; use lower initial dose in botulinum toxin naïve patients (2.8)
- Axillary Hyperhidrosis: 50 Units per axilla (2.9)
- Blepharospasm: 1.25 Units-2.5 Units into each of 3 sites per affected eye (2.10)
- Strabismus: The dose is based on prism diopter correction or previous response to treatment with BOTOX (2.11)

DOSAGE FORMS AND STRENGTHS

For Injection: 100 Units or 200 Units vacuum-dried powder in a single-dose vial (3)

CONTRAINDICATIONS

- Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation (4, 5.4, 6)
- Infection at the proposed injection site (4)
- Intradetrusor Injections: Urinary tract infection or urinary retention (4)

WARNINGS AND PRECAUTIONS

- Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur (5.1, 5.6)
- Potency Units of BOTOX are not interchangeable with other preparations of botulinum toxin products (5.2, 11)
- Potential serious adverse reactions after BOTOX injections for unapproved uses (5.3)
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment (5.5)
- Use with caution in patients with compromised respiratory function (5.6, 5.7, 5.10)
- Corneal exposure and ulceration due to reduced blinking may occur with BOTOX treatment of blepharospasm (5.8)
- Retrobulbar hemorrhages and compromised retinal circulation may occur with BOTOX treatment of strabismus (5.9)
- Bronchitis and upper respiratory tract infections in patients treated for spasticity (5.10)
- Urinary tract infections in patients treated for OAB (5.12)
- Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or adult detrusor overactivity associated with a neurologic condition who do not catheterize routinely, particularly patients with multiple sclerosis or diabetes mellitus. (5.13)

ADVERSE REACTIONS

The most common adverse reactions (≥5% and >placebo, if applicable) are (6.1):

- OAB: urinary tract infection, dysuria, urinary retention
- Adult Detrusor Overactivity associated with a neurologic condition: urinary tract infection, urinary retention
- Pediatric Detrusor Overactivity associated with a neurologic condition: urinary tract infection, leukocyturia, bacteriuria
- Chronic Migraine: neck pain, headache
- Adult Spasticity: pain in extremity
- Pediatric Spasticity: upper respiratory tract infection
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie at 1-800-678-1605 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Patients receiving concomitant treatment of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like agents), or muscle relaxants, should be observed closely because the effect of BOTOX may be potentiated (7.1, 7.4)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2023

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16 HOW SUPPLIED/STORAGE AND HANDLING

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17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. 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 treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses [see *Warnings and Precautions (5.1)*].

1 INDICATIONS AND USAGE**1.1 Adult Bladder Dysfunction***Overactive Bladder*

BOTOX for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Detrusor Overactivity associated with a Neurologic Condition

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

1.2 Pediatric Detrusor Overactivity Associated with a Neurologic Condition

BOTOX is indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication.

1.3 Chronic Migraine

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Limitations of Use

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

1.4 Spasticity

BOTOX is indicated for the treatment of spasticity in patients 2 years of age and older.

Limitations of Use

BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture.

1.5 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.6 Primary Axillary Hyperhidrosis

BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Limitations of Use

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

1.7 Blepharospasm and Strabismus

BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Safe Use

The potency Units of BOTOX (onabotulinumtoxinA) for injection are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [see *Warnings and Precautions (5.2) and Description (11)*].

Indication specific dosage and administration recommendations should be followed. When initiating treatment, the lowest recommended dose should be used. In treating adult patients for one or more indications, the maximum cumulative dose should not exceed 400 Units, in a 3-month interval. In pediatric patients, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval [see *Dosage and Administration (2.7)*].

The safe and effective use of BOTOX depends upon proper storage of the product, selection of the correct dose, and proper reconstitution and administration techniques. An understanding of standard electromyographic techniques is also required for treatment of strabismus, upper or lower limb spasticity, and may be useful for the treatment of cervical dystonia. Physicians administering BOTOX must understand the relevant neuromuscular and structural anatomy of the area involved and any alterations to the anatomy due to prior surgical procedures and disease, especially when injecting near the lungs.

Do not use BOTOX and contact AbbVie (1-800-678-1605) if:

- the tamper evident features on the carton appear to be broken or compromised, or
- the U.S. License number 1889 is not present on the vial label and carton labeling [see *How Supplied/Storage and Handling (16)*].

2.2 Preparation and Dilution Technique

Prior to injection, reconstitute each vacuum-dried vial of BOTOX with only sterile, preservative-free 0.9% Sodium Chloride Injection, USP. Draw up the proper amount of diluent in the appropriate size syringe (see Table 1, or for specific instructions for detrusor overactivity associated with a neurologic condition, see Section 2.3), and slowly inject the diluent into the vial. Discard the vial if a vacuum does not pull the diluent into the vial. Gently mix BOTOX with the diluent by rotating the vial. Record the date and time of reconstitution on the space on the label. BOTOX should be administered within 24 hours after reconstitution. During this time period, unused reconstituted BOTOX should be stored in a refrigerator (2° to 8°C) for up to 24 hours until time of use. BOTOX vials are for single-dose only. Discard any unused portion.

Table 1: Dilution Instructions for BOTOX Vials (100 Units and 200 Units)**

Diluent* Added to 100 Unit Vial	Resulting Dose Units per 0.1 mL	Diluent* Added to 200 Unit Vial	Resulting Dose Units per 0.1 mL
1 mL	10 Units	1 mL	20 Units
2 mL	5 Units	2 mL	10 Units
4 mL	2.5 Units	4 mL	5 Units
8 mL	1.25 Units	8 mL	2.5 Units
10 mL	1 Unit	10 mL	2 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

**For Detrusor Overactivity associated with a Neurologic Condition Dilution, see Section 2.3

Note: These dilutions are calculated for an injection volume of 0.1 mL. A decrease or increase in the BOTOX dose is also possible by administering a smaller or larger injection volume - from 0.05 mL (50% decrease in dose) to 0.15 mL (50% increase in dose).

An injection of BOTOX is prepared by drawing into an appropriately sized sterile syringe an amount of the properly reconstituted toxin slightly greater than the intended dose. Air bubbles in the syringe barrel are expelled and the syringe is attached to an appropriate injection needle. Patency of the needle should be confirmed. A new, sterile needle and syringe should be used to enter the vial on each occasion for removal of BOTOX.

Reconstituted BOTOX should be clear, colorless, and free of particulate matter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and whenever the solution and the container permit.

2.3 Adult Bladder Dysfunction

General

Patients must not have a urinary tract infection (UTI) at the time of treatment. Prophylactic antibiotics, except aminoglycosides, [see *Drug Interactions (7.1)*] should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment to reduce the likelihood of procedure-related UTI.

Patients should discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

Overactive Bladder

An intravesical instillation of diluted local anesthetic with or without sedation may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 100 Units of BOTOX, and is the maximum recommended dose. The recommended dilution is 100 Units/10 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Dispose of any unused saline.

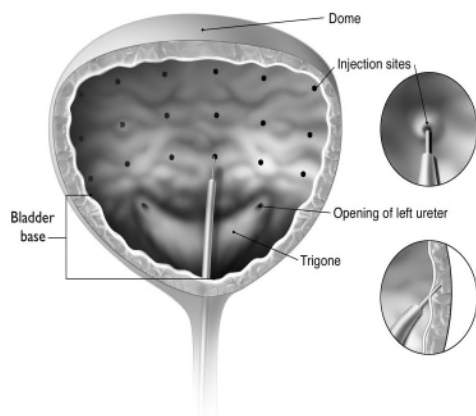
Reconstituted BOTOX (100 Units/10 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, patients should demonstrate their ability to void prior to leaving the clinic. The patient should be observed for at least 30 minutes post-injection and until a spontaneous void has occurred.

Patients should be considered for reinjection when the clinical effect of the previous injection has diminished (median time until patients qualified for the second treatment of BOTOX in double-blind, placebo-controlled clinical studies was 169 days [~24 weeks]), but no sooner than 12 weeks from the prior bladder injection.

Figure 1: Injection Pattern for Intradetrusor Injections for Treatment of Overactive Bladder and Detrusor Overactivity Associated with a Neurologic Condition



Detrusor Overactivity associated with a Neurologic Condition

An intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia may be used prior to injection, per local site practice. If a local anesthetic instillation is performed, the bladder should be drained and irrigated with sterile saline before injection.

The recommended dose is 200 Units of BOTOX per treatment, and should not be exceeded.

200 Unit Vial of BOTOX

- Reconstitute a 200 Unit vial of BOTOX with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
- Draw 2 mL from the vial into each of three 10 mL syringes.
- Complete the reconstitution by adding 8 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

100 Unit Vial of BOTOX

- Reconstitute two 100 Unit vials of BOTOX, each with 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vials gently.
- Draw 4 mL from each vial into each of two 10 mL syringes. Draw the remaining 2 mL from each vial into a third 10 mL syringe for a total of 4 mL in each syringe.
- Complete the reconstitution by adding 6 mL of preservative-free 0.9% Sodium Chloride Injection, USP into each of the 10 mL syringes, and mix gently. This will result in three 10 mL syringes each containing 10 mL (~67 Units in each), for a total of 200 Units of reconstituted BOTOX.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

Reconstituted BOTOX (200 Units/30 mL) is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 30 injections of 1 mL (~6.7 Units) each (total volume of 30 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, placebo-controlled clinical studies was 295-337 days [42-48 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

2.4 Pediatric Detrusor Overactivity Associated with a Neurologic Condition

Patients must not have a urinary tract infection (UTI) at the time of treatment. Oral prophylactic antibiotics, except aminoglycosides, [see *Drug Interactions (7.1)*] should be administered 1-3 days pre-treatment, on the treatment day, and 1-3 days post-treatment to reduce the likelihood of procedure-related UTI. Alternatively, for patients receiving general anesthesia (or conscious sedation) for the treatment of detrusor overactivity associated with a neurologic condition, one dose of IV prophylactic antibiotics, except aminoglycosides, [see *Drug Interactions (7.1)*] may be administered prior to treatment administration on the day of treatment.

Patients should discontinue anti-platelet therapy at least 3 days before the injection procedure. Patients on anti-coagulant therapy need to be managed appropriately to decrease the risk of bleeding.

Appropriate caution should be exercised when performing a cystoscopy.

- In patients 5 years to less than 12 years of age: Consider general anesthesia (or conscious sedation) prior to injection, per local site practice.
- In patients 12 years of age or older: Consider an intravesical instillation of diluted local anesthetic with or without sedation, or general anesthesia prior to injection, per local site practice.

At a minimum, consider a diluted instillation of local anesthetic for all age groups. If a local anesthetic instillation is performed, drain and irrigate the bladder with sterile saline before injection.

If patient's body weight is greater than or equal to 34 kg, the recommended dosage is 200 Units of BOTOX per treatment administered as an intradetrusor injection after dilution:

- Reconstitute BOTOX to result in 20 Units BOTOX/mL in the vial(s):
 - BOTOX 200 Unit vial: add 10 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.

- BOTOX 100 Unit vials: add 5 mL of preservative-free 0.9% Sodium Chloride Injection, USP to each of two 100 Unit vials of BOTOX and mix the vials gently.
- Draw 10 mL from the vial(s) into one 10 mL dosing syringe.
- Use immediately after reconstitution in the syringe. Dispose of any unused saline.

If patient's body weight is less than 34 kg, the recommended dosage is 6 Units/kg body weight administered as a bladder injection after dilution (refer to Table 2):

- Reconstitute BOTOX to result in 20 Units BOTOX/mL in the vial(s):
 - BOTOX 200 Unit vial: add 10 mL of preservative-free 0.9% Sodium Chloride Injection, USP and mix the vial gently.
 - BOTOX 100 Unit vial(s): add 5 mL of preservative-free 0.9% Sodium Chloride Injection, USP to one 100 Unit vial of BOTOX (if final dose is less than or equal to 100 U) or to each of two 100 Unit vials of BOTOX (if final dose is greater than 100 U) and mix the vial(s) gently.
- Refer to Table 2 for dilution instructions (i.e., the amount of reconstituted BOTOX and additional diluent to draw into one 10 mL dosing syringe).
- Use BOTOX immediately after reconstitution in the syringe. Dispose of any unused preservative-free 0.9% Sodium Chloride Injection, USP.

Table 2: BOTOX Dilution Instructions and Final Dosing for Patients with Body Weight < 34 kg

Body Weight (kg)	Volume of reconstituted BOTOX and Diluent* (mL) to draw into dosing syringe to achieve a final volume of 10 mL		Final dose of BOTOX in dosing syringe
	BOTOX (mL)	Diluent* (mL)	
12 to less than 14	3.6	6.4	72 Units
14 to less than 16	4.2	5.8	84 Units
16 to less than 18	4.8	5.2	96 Units
18 to less than 20	5.4	4.6	108 Units
20 to less than 22	6	4	120 Units
22 to less than 24	6.6	3.4	132 Units
24 to less than 26	7.2	2.8	144 Units
26 to less than 28	7.8	2.2	156 Units
28 to less than 30	8.4	1.6	168 Units
30 to less than 32	9	1	180 Units
32 to less than 34	9.6	0.4	192 Units

*Preservative-free 0.9% Sodium Chloride Injection, USP Only

Reconstituted BOTOX is injected into the detrusor muscle via a flexible or rigid cystoscope, avoiding the trigone. The bladder should be instilled with enough saline to achieve adequate visualization for the injections, but over-distension should be avoided.

The injection needle should be filled (primed) with approximately 1 mL of reconstituted BOTOX prior to the start of injections (depending on the needle length) to remove any air.

The needle should be inserted approximately 2 mm into the detrusor, and 20 injections of 0.5 mL each (total volume of 10 mL) should be spaced approximately 1 cm apart (see Figure 1). For the final injection, approximately 1 mL of sterile normal saline should be injected so that the remaining BOTOX in the needle is delivered to the bladder. After the injections are given, the saline used for bladder wall visualization should be drained. The patient should be observed for at least 30 minutes post-injection.

Patients should be considered for re-injection when the clinical effect of the previous injection diminishes (median time to qualification for re-treatment in the double-blind, parallel group clinical study was 207 days [30 weeks] for BOTOX 200 Units), but no sooner than 12 weeks from the prior bladder injection.

2.5 Chronic Migraine

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL, with a final concentration of 5 Units per 0.1 mL (see Table 1). The recommended dose for treating chronic migraine is 155 Units administered intramuscularly using a sterile 30-gauge, 0.5 inch needle as 0.1 mL (5 Units) injections per each site. Injections should be divided across 7 specific head/neck muscle areas as specified in the diagrams and Table 3 below. A one inch needle may be needed in the neck region for patients with thick neck muscles. With the exception of the procerus muscle, which should be injected at one site (midline), all muscles should be injected bilaterally with half the number of injection sites administered to the left, and half to the right side of the head and neck. The recommended re-treatment schedule is every 12 weeks.

Diagrams 1-4: Recommended Injection Sites (A through G) for Chronic Migraine

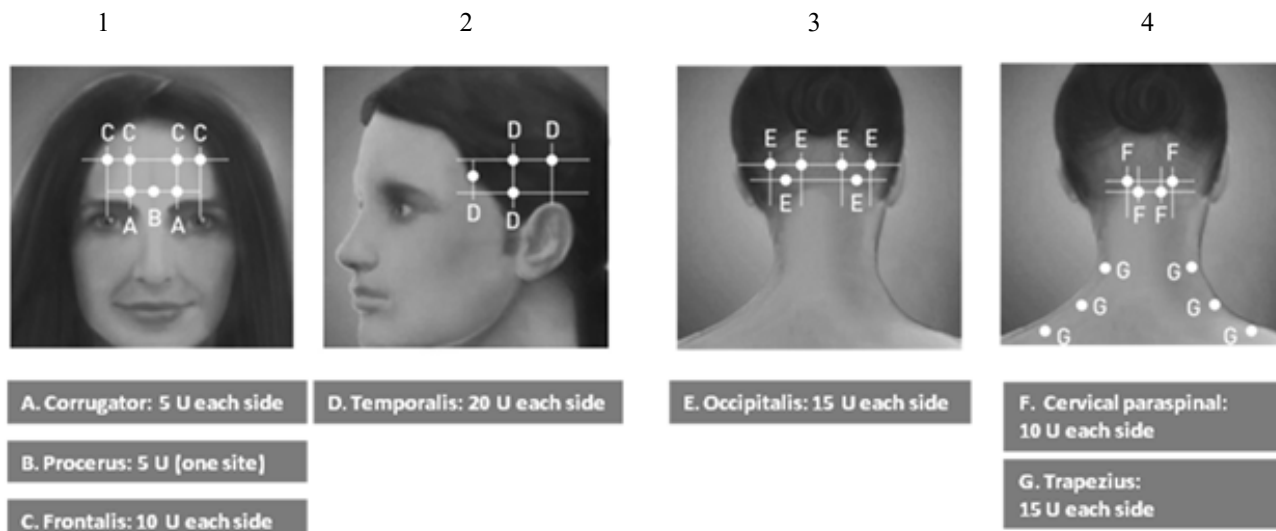


Table 3: BOTOX Dosing by Muscle for Chronic Migraine

Head/Neck Area	Recommended Dose (Number of Sites ^a)
Frontalis ^b	20 Units divided in 4 sites
Corrugator ^b	10 Units divided in 2 sites
Procerus	5 Units in 1 site
Occipitalis ^b	30 Units divided in 6 sites
Temporalis ^b	40 Units divided in 8 sites
Trapezius ^b	30 Units divided in 6 sites
Cervical Paraspinal Muscle Group ^b	20 Units divided in 4 sites
Total Dose:	155 Units divided in 31 sites

^a Each IM injection site = 0.1 mL = 5 Units BOTOX

^b Dose distributed bilaterally

2.6 Adult Spasticity

General

Dosing in initial and sequential treatment sessions should be tailored to the individual based on the size, number and location of muscles involved, severity of spasticity, the presence of local muscle weakness, the patient's response to previous treatment, or adverse event history with BOTOX.

The recommended dilution is 200 Units/4 mL or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). The lowest recommended starting dose should be used, and no more than 50 Units per site should generally be administered. An appropriately sized needle (e.g., 25-30 gauge) may be used for superficial muscles, and a longer 22 gauge needle may be used for deeper musculature. Localization of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended.

Repeat BOTOX treatment may be administered when the effect of a previous injection has diminished, but generally no sooner than 12 weeks after the previous injection. The degree and pattern of muscle spasticity at the time of re-injection may necessitate alterations in the dose of BOTOX and muscles to be injected.

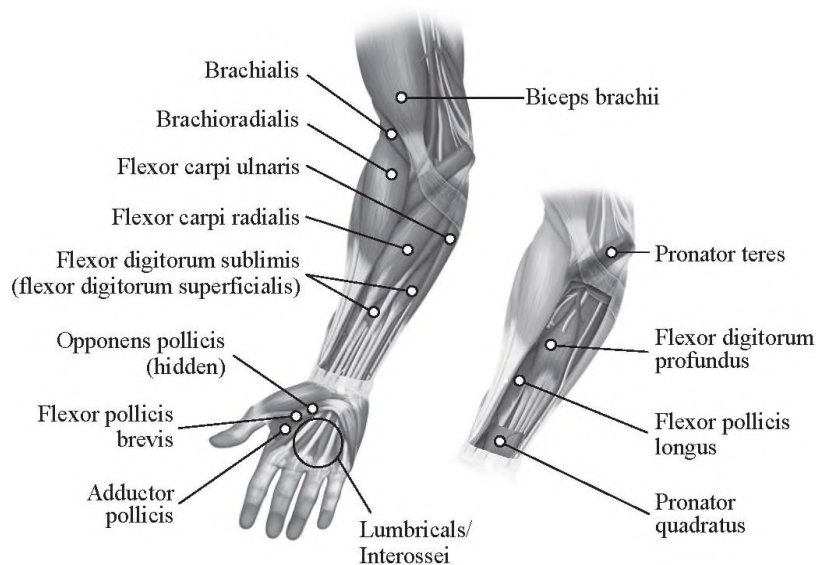
Adult Upper Limb Spasticity

In clinical trials, doses ranging from 75 Units to 400 Units were divided among selected muscles (see Table 4 and Figure 2) at a given treatment session.

Table 4: BOTOX Dosing by Muscle for Adult Upper Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Biceps Brachii	60 Units to 200 Units divided in 2 to 4 sites
Brachioradialis	45 Units to 75 Units divided in 1 to 2 sites
Brachialis	30 Units to 50 Units divided in 1 to 2 sites
Pronator Teres	15 Units to 25 Units in 1 site
Pronator Quadratus	10 Units to 50 Units in 1 site
Flexor Carpi Radialis	12.5 Units to 50 Units in 1 site
Flexor Carpi Ulnaris	12.5 Units to 50 Units in 1 site
Flexor Digitorum Profundus	30 Units to 50 Units in 1 site
Flexor Digitorum Sublimis	30 Units to 50 Units in 1 site
Lumbricals/Interossei	5 Units to 10 Units in 1 site
Adductor Pollicis	20 Units in 1 site
Flexor Pollicis Longus	20 Units in 1 site
Flexor pollicis brevis/ Opponens pollicis	5 Units to 25 Units in 1 site

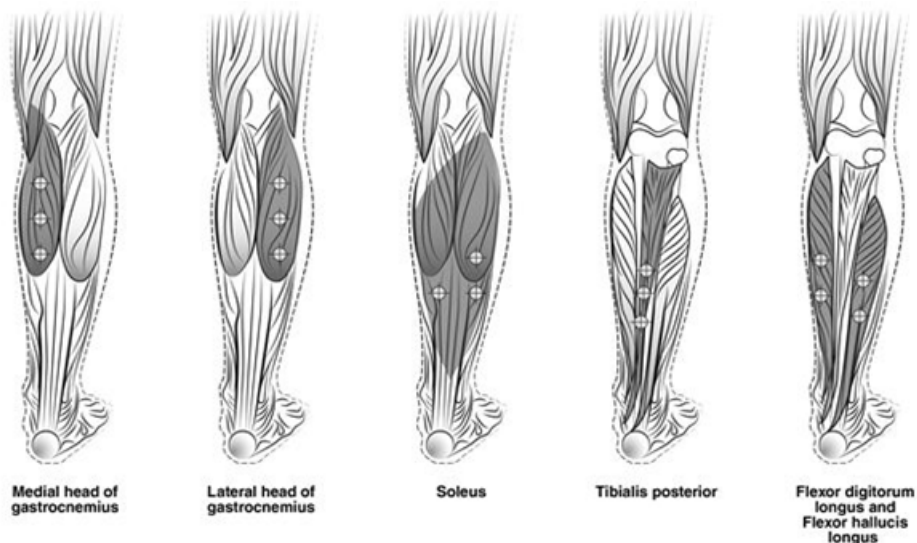
Figure 2: Injection Sites for Adult Upper Limb Spasticity

*Adult Lower Limb Spasticity*

The recommended dose for treating adult lower limb spasticity is 300 Units to 400 Units divided among 5 muscles (gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and flexor digitorum longus) (see Table 5 and Figure 3).

Table 5: BOTOX Dosing by Muscle for Adult Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Gastrocnemius medial head	75 Units divided in 3 sites
Gastrocnemius lateral head	75 Units divided in 3 sites
Soleus	75 Units divided in 3 sites
Tibialis Posterior	75 Units divided in 3 sites
Flexor hallucis longus	50 Units divided in 2 sites
Flexor digitorum longus	50 Units divided in 2 sites

Figure 3: Injection Sites for Adult Lower Limb Spasticity

2.7 Pediatric Spasticity

General

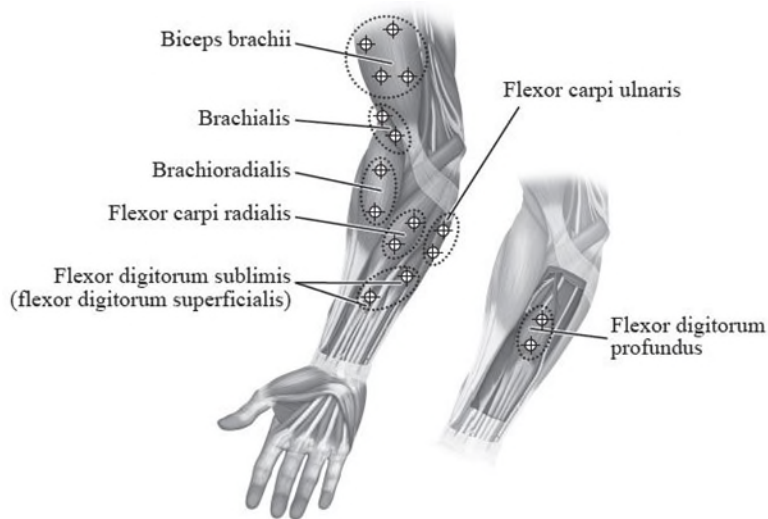
Localization of the involved muscles with techniques such as needle electromyographic guidance, nerve stimulation, or ultrasound is recommended. When treating both lower limbs or the upper and lower limbs in combination, the total dose should not exceed the lower of 10 Units/kg body weight or 340 Units, in a 3-month interval [see *Boxed Warning and Warnings and Precautions (5.1, 5.6)*]. Additional general adult spasticity dosing information is also applicable to pediatric spasticity patients [see *Dosage and Administration (2.6)*].

Pediatric Upper Limb Spasticity

The recommended dose for treating pediatric upper limb spasticity is 3 Units/kg to 6 Units/kg divided among the affected muscles (see Table 6 and Figure 4). The total dose of BOTOX administered per treatment session in the upper limb should not exceed 6 Units/kg or 200 Units, whichever is lower.

Table 6: BOTOX Dosing by Muscle for Pediatric Upper Limb Spasticity

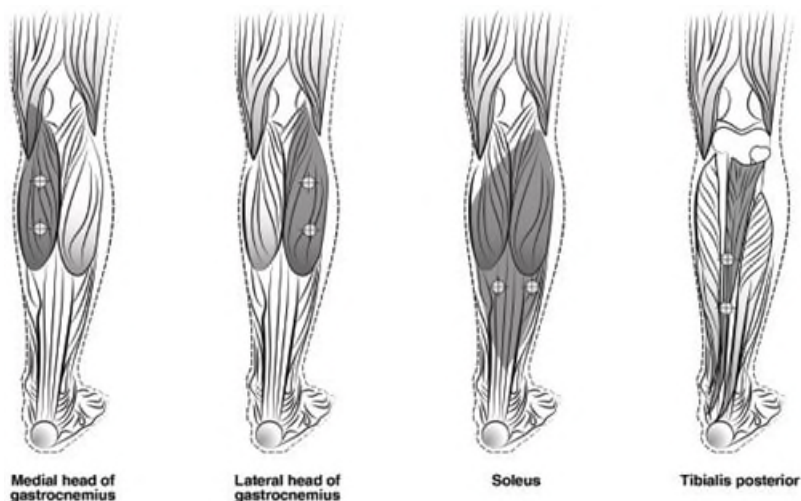
Muscle	Recommended Dose and Number of Sites
Biceps Brachii	1.5 Units/kg to 3 Units/kg divided in 4 sites
Brachialis	1 Unit/kg to 2 Units/kg divided in 2 sites
Brachioradialis	0.5 Units/kg to 1 Unit/kg divided in 2 sites
Flexor Carpi Radialis	1 Unit/kg to 2 Units/kg divided in 2 sites
Flexor Carpi Ulnaris	1 Unit/kg to 2 Units/kg divided in 2 sites
Flexor Digitorum Profundus	0.5 Units/kg to 1 Unit/kg divided in 2 sites
Flexor Digitorum Sublimis	0.5 Units/kg to 1 Unit/kg divided in 2 sites

Figure 4: Injection Sites for Pediatric Upper Limb Spasticity*Pediatric Lower Limb Spasticity*

The recommended dose for treating pediatric lower limb spasticity is 4 Units/kg to 8 Units/kg divided among the affected muscles (see Table 7 and Figure 5). The total dose of BOTOX administered per treatment session in the lower limb should not exceed 8 Units/kg or 300 Units, whichever is lower.

Table 7: BOTOX Dosing by Muscle for Pediatric Lower Limb Spasticity

Muscle	Recommended Dose Total Dosage (Number of Sites)
Gastrocnemius medial head	1 Unit/kg to 2 Units/kg divided in 2 sites
Gastrocnemius lateral head	1 Unit/kg to 2 Units/kg divided in 2 sites
Soleus	1 Unit/kg to 2 Units/kg divided in 2 sites
Tibialis Posterior	1 Unit/kg to 2 Units/kg divided in 2 sites

Figure 5: Injection Sites for Pediatric Lower Limb Spasticity

2.8 Cervical Dystonia

A double-blind, placebo-controlled study enrolled patients who had extended histories of receiving and tolerating BOTOX injections, with prior individualized adjustment of dose. The mean BOTOX dose administered to patients in this study was 236 Units (25th to 75th percentile range of 198 Units to 300 Units). The BOTOX dose was divided among the affected muscles [see *Clinical Studies* (14.7)].

Dosing in initial and sequential treatment sessions should be tailored to the individual patient based on the patient's head and neck position, localization of pain, muscle hypertrophy, patient response, and adverse event history. The initial dose for a patient without prior use of BOTOX should be at a lower dose, with subsequent dosing adjusted based on individual response. Limiting the total dose injected into the sternocleidomastoid muscle to 100 Units or less may decrease the occurrence of dysphagia [see *Warnings and Precautions* (5.1, 5.5, 5.6)].

The recommended dilution is 200 Units/2 mL, 200 Units/4 mL, 100 Units/1 mL, or 100 Units/2 mL with preservative-free 0.9% Sodium Chloride Injection, USP, depending on volume and number of injection sites desired to achieve treatment objectives (see Table 1). In general, no more than 50 Units per site should be administered using a sterile needle (e.g., 25-30 gauge) of an appropriate length. Localization of the involved muscles with electromyographic guidance may be useful.

Clinical improvement generally begins within the first two weeks after injection with maximum clinical benefit at approximately six weeks post-injection. In the double-blind, placebo-controlled study most subjects were observed to have returned to pre-treatment status by 3 months post-treatment.

2.9 Primary Axillary Hyperhidrosis

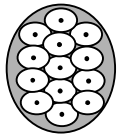
The recommended dose is 50 Units per axilla. The hyperhidrotic area to be injected should be defined using standard staining techniques, e.g., Minor's Iodine-Starch Test. The recommended dilution is 100 Units/4 mL with preservative-free 0.9% Sodium Chloride Injection, USP (see Table 1). Using a sterile 30 gauge needle, 50 Units of BOTOX (2 mL) is injected intradermally in 0.1 to 0.2 mL aliquots to each axilla evenly distributed in multiple sites (10-15) approximately 1-2 cm apart.

Repeat injections for hyperhidrosis should be administered when the clinical effect of a previous injection diminishes.

Instructions for the Minor's Iodine-Starch Test Procedure:

Patients should shave underarms and abstain from use of over-the-counter deodorants or antiperspirants for 24 hours prior to the test. Patient should be resting comfortably without exercise or hot drinks for approximately 30 minutes prior to the test. Dry the underarm area and then immediately paint it with iodine solution. Allow the area to dry, then lightly sprinkle the area with starch powder. Gently blow off any excess starch powder. The hyperhidrotic area will develop a deep blue-black color over approximately 10 minutes.

Each injection site has a ring of effect of up to approximately 2 cm in diameter. To minimize the area of no effect, the injection sites should be evenly spaced as shown in Figure 6.

Figure 6: Injection Pattern for Primary Axillary Hyperhidrosis

Each dose is injected to a depth of approximately 2 mm and at a 45° angle to the skin surface, with the bevel side up to minimize leakage and to ensure the injections remain intradermal. If injection sites are marked in ink, do not inject BOTOX directly through the ink mark to avoid a permanent tattoo effect.

2.10 Blepharospasm

For blepharospasm, reconstituted BOTOX is injected using a sterile, 27-30 gauge needle without electromyographic guidance. The initial recommended dose is 1.25 Units-2.5 Units (0.05 mL to 0.1 mL volume at each site) injected into the medial and lateral pre-tarsal orbicularis oculi of the upper lid and into the lateral pre-tarsal orbicularis oculi of the lower lid. Avoiding injection near the levator palpebrae superioris may reduce the complication of ptosis. Avoiding medial lower lid injections, and thereby reducing diffusion into the inferior oblique, may reduce the complication of diplopia. Ecchymosis occurs easily in the soft eyelid tissues. This can be prevented by applying pressure at the injection site immediately after the injection.

The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Table 1).

In general, the initial effect of the injections is seen within three days and reaches a peak at one to two weeks post-treatment. Each treatment lasts approximately three months, following which the procedure can be repeated. At repeat treatment sessions, the dose may be increased up to two-fold if the response from the initial treatment is considered insufficient, usually defined as an effect that does not last longer than two months. However, there appears to be little benefit obtainable from injecting more than 5 Units per site. Some tolerance may be found when BOTOX is used in treating blepharospasm if treatments are given any more frequently than every three months, and is rare to have the effect be permanent.

The cumulative dose of BOTOX treatment for blepharospasm in a 30-day period should not exceed 200 Units.

2.11 Strabismus

BOTOX is intended for injection into extraocular muscles utilizing the electrical activity recorded from the tip of the injection needle as a guide to placement within the target muscle. Injection without surgical exposure or electromyographic guidance should not be attempted. Physicians should be familiar with electromyographic technique.

To prepare the eye for BOTOX injection, it is recommended that several drops of a local anesthetic and an ocular decongestant be given several minutes prior to injection.

The volume of BOTOX injected for treatment of strabismus should be between 0.05-0.15 mL per muscle.

The initial listed doses of the reconstituted BOTOX [see *Dosage and Administration (2.2)*] typically create paralysis of the injected muscles beginning one to two days after injection and increasing in intensity during the first week. The paralysis lasts for 2-6 weeks and gradually resolves over a similar time period. Overcorrections lasting over six months have been rare. About one half of patients will require subsequent doses because of inadequate paralytic response of the muscle to the initial dose, or because of mechanical factors such as large deviations or restrictions, or because of the lack of binocular motor fusion to stabilize the alignment.

Initial Doses in Units

Use the lower listed doses for treatment of small deviations. Use the larger doses only for large deviations.

- For vertical muscles, and for horizontal strabismus of less than 20 prism diopters: 1.25 Units-2.5 Units in any one muscle.
- For horizontal strabismus of 20 prism diopters to 50 prism diopters: 2.5 Units-5 Units in any one muscle.
- For persistent VI nerve palsy of one month or longer duration: 1.25 Units-2.5 Units in the medial rectus muscle.

Subsequent Doses for Residual or Recurrent Strabismus

- It is recommended that patients be re-examined 7-14 days after each injection to assess the effect of that dose.
- Patients experiencing adequate paralysis of the target muscle that require subsequent injections should receive a dose comparable to the initial dose.
- Subsequent doses for patients experiencing incomplete paralysis of the target muscle may be increased up to two-fold compared to the previously administered dose.
- Subsequent injections should not be administered until the effects of the previous dose have dissipated as evidenced by substantial function in the injected and adjacent muscles.
- The maximum recommended dose as a single injection for any one muscle is 25 Units.

The recommended dilution to achieve 1.25 Units is 100 Units/8 mL; for 2.5 Units it is 100 Units/4 mL (see Table 1).

3 DOSAGE FORMS AND STRENGTHS

For Injection: sterile 100 Units or 200 Units vacuum-dried powder in single-dose vials for reconstitution only with sterile, preservative-free 0.9% Sodium Chloride Injection, USP prior to injection.

4 CONTRAINDICATIONS

BOTOX is contraindicated:

- In patients who are hypersensitive to any botulinum toxin product or to any of the components in the formulation [*see Warnings and Precautions (5.4)*].
- In the presence of infection at the proposed injection site(s).
- For intradetrusor injection in patients with a urinary tract infection; or in patients with urinary retention or post-void residual (PVR) urine volume >200 mL who are not routinely performing clean intermittent self-catheterization (CIC) [*see Warnings and Precautions (5.12, 5.13)*].

5 WARNINGS AND PRECAUTIONS

5.1 Spread of Toxin Effect

Postmarketing safety data from BOTOX and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. 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 related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX for blepharospasm at the recommended dose (30 Units and below), severe primary axillary hyperhidrosis at the recommended dose (100 Units), strabismus, or for chronic migraine at the labeled doses have been reported.

5.2 Lack of Interchangeability between Botulinum Toxin Products

The potency Units of BOTOX are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method [*see Description (11)*].

5.3 Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX. The safety and effectiveness of BOTOX for unapproved uses have not been established.

5.4 Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

5.5 Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects

including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of BOTOX [see *Warnings and Precautions* (5.1, 5.6)].

5.6 Dysphagia and Breathing Difficulties

Treatment with BOTOX 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. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing [see *Warnings and Precautions* (5.1)].

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin [see *Warnings and Precautions* (5.1)].

5.7 Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated with a Neurologic Condition

Patients with compromised respiratory status treated with BOTOX for spasticity should be monitored closely. In a double-blind, placebo-controlled, parallel group study in adult patients treated for upper limb spasticity with stable reduced pulmonary function (defined as FEV₁ 40-80% of predicted value and FEV₁/FVC \leq 0.75), the event rate in change of Forced Vital Capacity (FVC) \geq 15% or \geq 20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 8).

Table 8: Event Rate Per Patient Treatment Cycle Among Adult Upper Limb Spasticity Patients with Reduced Lung Function Who Experienced at Least a 15% or 20% Decrease in FVC From Baseline at Week 1, 6, 12 Post-injection with Up to Two Treatment Cycles with BOTOX or Placebo

	BOTOX 360 Units		BOTOX 240 Units		Placebo	
	\geq 15%	\geq 20%	\geq 15%	\geq 20%	\geq 15%	\geq 20%
Week 1	4%	0%	3%	0%	7%	3%
Week 6	7%	4%	4%	2%	2%	2%
Week 12	10%	5%	2%	1%	4%	1%

Differences from placebo were not statistically significant

In adult spasticity patients with reduced lung function, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX than in patients treated with placebo [see *Warnings and Precautions* (5.10)].

In a double-blind, placebo-controlled, parallel group study in adult patients with detrusor overactivity associated with a neurologic condition and restrictive lung disease of neuromuscular etiology [defined as FVC 50-80% of predicted value in patients with spinal cord injury between C5 and C8, or MS] the event rate in change of Forced Vital Capacity \geq 15% or \geq 20% was generally greater in patients treated with BOTOX than in patients treated with placebo (see Table 9).

Table 9: Number and Percent of Patients Experiencing at Least a 15% or 20% Decrease in FVC From Baseline at Week 2, 6, 12 Post-Injection with BOTOX or Placebo

	BOTOX 200 Units		Placebo	
	$\geq 15\%$	$\geq 20\%$	$\geq 15\%$	$\geq 20\%$
Week 2	0/15 (0%)	0/15 (0%)	1/11 (9%)	0/11 (0%)
Week 6	2/13 (15%)	1/13 (8%)	0/12 (0%)	0/12 (0%)
Week 12	0/12(0%)	0/12 (0%)	0/7 (0%)	0/7 (0%)

5.8 Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm

Reduced blinking from BOTOX injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect, and corneal ulceration, especially in patients with VII nerve disorders. Vigorous treatment of any epithelial defect should be employed. This may require protective drops, ointment, therapeutic soft contact lenses, or closure of the eye by patching or other means.

5.9 Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus

During the administration of BOTOX for the treatment of strabismus, retrobulbar hemorrhages sufficient to compromise retinal circulation have occurred. It is recommended that appropriate instruments to decompress the orbit be accessible.

5.10 Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity

Bronchitis was reported more frequently as an adverse reaction in adult patients treated for upper limb spasticity with BOTOX (3% at 251 Units-360 Units total dose), compared to placebo (1%). In adult patients with reduced lung function treated for upper limb spasticity, upper respiratory tract infections were also reported more frequently as adverse reactions in patients treated with BOTOX (11% at 360 Units total dose; 8% at 240 Units total dose) compared to placebo (6%). In adult patients treated for lower limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (2% at 300 Units to 400 Units total dose) compared to placebo (1%). In pediatric patients treated for upper limb spasticity, upper respiratory tract infections were reported more frequently as an adverse reaction in patients treated with BOTOX (17% at 6 Units/kg and 10% at 3 Units/kg) compared to placebo (9%). In pediatric patients treated for lower limb spasticity, upper respiratory tract infection was not reported with an incidence greater than placebo.

5.11 Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity Associated with a Neurologic Condition

Autonomic dysreflexia associated with intradetrusor injections of BOTOX could occur in patients treated for detrusor overactivity associated with a neurologic condition and may require prompt medical therapy. In clinical trials, the incidence of autonomic dysreflexia was greater in adult patients treated with BOTOX 200 Units compared with placebo (1.5% versus 0.4%, respectively).

5.12 Urinary Tract Infections in Patients with Overactive Bladder

BOTOX increases the incidence of urinary tract infection [see *Adverse Reactions (6.1)*]. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

5.13 Urinary Retention in Adults Treated for Bladder Dysfunction

Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post-treatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

The incidence and duration of urinary retention is described below for adult patients with overactive bladder and detrusor overactivity associated with a neurologic condition who received BOTOX or placebo injections.

Overactive Bladder

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated clean intermittent catheterization (CIC) for urinary retention following treatment with BOTOX or placebo is shown in Table 10. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 10: Proportion of Patients Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB

Timepoint	BOTOX 100 Units (N=552)	Placebo (N=542)
Proportion of Patients Catheterizing for Urinary Retention		
At any time during complete treatment cycle	6.5% (n=36)	0.4% (n=2)
Duration of Catheterization for Urinary Retention (Days)		
Median	63	11
Min, Max	1, 214	3, 18

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those without diabetes, as shown in Table 11.

Table 11: Proportion of Patients Experiencing Urinary Retention Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB According to History of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81)	Placebo (N=69)	BOTOX 100 Units (N=526)	Placebo (N=516)
Urinary retention	12.3% (n=10)	0	6.3% (n=33)	0.6% (n=3)

Adult Detrusor Overactivity associated with a Neurologic Condition

In two double-blind, placebo-controlled trials in adult patients with detrusor overactivity associated with a neurologic condition (NDO-1 and NDO-2), the proportion of subjects who were not using clean intermittent catheterization (CIC) prior to injection and who subsequently required catheterization for urinary retention following treatment with BOTOX 200 Units or placebo is shown in Table 12. The duration of post-injection catheterization for those who developed urinary retention is also shown.

Table 12: Proportion of Adult Patients Not Using CIC at Baseline and then Catheterizing for Urinary Retention and Duration of Catheterization Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials

Timepoint	BOTOX 200 Units (N=108)	Placebo (N=104)
Proportion of Patients Catheterizing for Urinary Retention		
At any time during complete treatment cycle	30.6% (n=33)	6.7% (n=7)
Duration of Catheterization for Urinary Retention (Days)		
Median	289	358
Min, Max	1, 530	2, 379

Among adult patients not using CIC at baseline, those with Multiple Sclerosis (MS) were more likely to require CIC post-injection than those with Spinal Cord Injury (SCI) (see Table 13).

Table 13: Proportion of Adult Patients by Etiology (MS and SCI) Not Using CIC at Baseline and then Catheterizing for Urinary Retention Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials

Timepoint	MS		SCI	
	BOTOX 200 Units (N=86)	Placebo (N=88)	BOTOX 200 Units (N=22)	Placebo (N=16)
At any time during complete treatment cycle	31% (n=27)	5% (n=4)	27% (n=6)	19% (n=3)

A placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) was conducted in non-catheterizing adult MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. Catheterization for urinary retention was initiated in 15.2% (10/66) of patients following treatment with BOTOX 100 Units versus 2.6% (2/78) on placebo at any time during the complete treatment cycle. The median duration of post-injection catheterization for those who developed urinary retention was 64 days for BOTOX 100 Units and 2 days for placebo.

5.14 Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. 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 identified for licensed albumin or albumin contained in other licensed products.

6 ADVERSE REACTIONS

The following adverse reactions to BOTOX (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions (5.1)]*
- Serious Adverse Reactions with Unapproved Use *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Contraindications (4) and Warnings and Precautions (5.4)]*
- Increased Risk of Clinically Significant Effects with Pre-Existing Neuromuscular Disorders *[see Warnings and Precautions (5.5)]*
- Dysphagia and Breathing Difficulties *[see Warnings and Precautions (5.6)]*
- Pulmonary Effects of BOTOX in Patients with Compromised Respiratory Status Treated for Spasticity or for Detrusor Overactivity Associated with a Neurologic Condition *[see Warnings and Precautions (5.7)]*
- Corneal Exposure and Ulceration in Patients Treated with BOTOX for Blepharospasm *[see Warnings and Precautions (5.8)]*
- Retrobulbar Hemorrhages in Patients Treated with BOTOX for Strabismus *[see Warnings and Precautions (5.9)]*
- Bronchitis and Upper Respiratory Tract Infections in Patients Treated for Spasticity *[see Warnings and Precautions (5.10)]*
- Autonomic Dysreflexia in Patients Treated for Detrusor Overactivity Associated with a Neurologic Condition *[see Warnings and Precautions (5.11)]*
- Urinary Tract Infections in Patients with Overactive Bladder *[see Warnings and Precautions (5.12)]*
- Urinary Retention in Patients Treated for Bladder Dysfunction *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse reactions observed with the use of BOTOX Cosmetic also have the potential to be observed with the use of BOTOX.

In general, adverse reactions occur within the first week following injection of BOTOX and, while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Symptoms associated with flu-like symptoms (e.g., nausea, fever, myalgia) have been reported after treatment. Needle-related pain and/or anxiety may result in vasovagal responses (including syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions (5.1)]*.

Overactive Bladder

Table 14 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 14: Adverse Reactions Reported by $\geq 2\%$ of BOTOX Treated Patients and More Often than in Placebo-Treated Patients Within the First 12 Weeks after Intradetrusor Injection, in Double-Blind, Placebo-Controlled Clinical Trials in Patients with OAB

Adverse Reactions	BOTOX 100 Units (N=552) %	Placebo (N=542) %
Urinary tract infection	18	6
Dysuria	9	7
Urinary retention	6	0
Bacteriuria	4	2
Residual urine volume*	3	0

*Elevated PVR not requiring catheterization. Catheterization was required for PVR ≥ 350 mL regardless of symptoms, and for PVR ≥ 200 mL to <350 mL with symptoms (e.g., voiding difficulty).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 Units and placebo than in patients without diabetes, as shown in Table 15.

Table 15: Proportion of Patients Experiencing Urinary Tract Infection Following an Injection in Double-Blind, Placebo-Controlled Clinical Trials in OAB According to History of Diabetes Mellitus

	Patients with Diabetes		Patients without Diabetes	
	BOTOX 100 Units (N=81) %	Placebo (N=69) %	BOTOX 100 Units (N=526) %	Placebo (N=516) %
Urinary tract infection (UTI)	31	12	26	10

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥ 200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% versus 23%, respectively. No change was observed in the overall safety profile with repeat dosing during an open-label, uncontrolled extension trial.

Adult Detrusor Overactivity associated with a Neurologic Condition

Table 16 presents the most frequently reported adverse reactions in the double-blind, placebo-controlled studies within 12 weeks of injection for patients with detrusor overactivity associated with a neurologic condition treated with BOTOX 200 Units.

Table 16: Adverse Reactions Reported by $\geq 2\%$ of BOTOX-Treated Patients and More Frequent than in Placebo-Treated Patients Within the First 12 Weeks after Intradetrusor Injection in Double-Blind, Placebo-Controlled Clinical Trials

Adverse Reactions	BOTOX 200 Units (N=262) %	Placebo (N=272) %
Urinary tract infection	24	17
Urinary retention	17	3
Hematuria	4	3

The following adverse reactions with BOTOX 200 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 44 weeks): urinary tract infections (49%), urinary retention (17%), constipation (4%), muscular weakness (4%), dysuria (4%), fall (3%), gait disturbance (3%), and muscle spasm (2%).

In the Multiple Sclerosis (MS) patients enrolled in the double-blind, placebo-controlled trials, the MS exacerbation annualized rate (i.e., number of MS exacerbation events per patient-year) was 0.23 for BOTOX and 0.20 for placebo.

No change was observed in the overall safety profile with repeat dosing.

Table 17 presents the most frequently reported adverse reactions in a placebo-controlled, double-blind post-approval 52 week study with BOTOX 100 Units (Study NDO-3) conducted in MS patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least one anticholinergic agent and not catheterized at baseline. The table below presents the most frequently reported adverse reactions within 12 weeks of injection.

Table 17: Adverse Reactions Reported in a Post Approval Study (NDO-3) by >2% of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients Within the First 12 Weeks after Intradetrusor Injection

Adverse Reactions	BOTOX 100 Units (N=66) %	Placebo (N=78) %
Urinary tract infection	26	6
Bacteriuria	9	5
Urinary retention	15	1
Dysuria	5	1
Residual urine volume*	17	1

* Elevated PVR not requiring catheterization. Catheterization was required for PVR ≥ 350 mL regardless of symptoms, and for PVR ≥ 200 mL to < 350 mL with symptoms (e.g., voiding difficulty).

The following adverse events with BOTOX 100 Units were reported at any time following initial injection and prior to re-injection or study exit (median duration of exposure was 51 weeks): urinary tract infections (39%), bacteriuria (18%), urinary retention (17%), residual urine volume* (17%), dysuria (9%), and hematuria (5%).

No difference in the MS exacerbation annualized rate (i.e., number of MS exacerbating events per patient-year) was observed (BOTOX =0, placebo =0.07).

Pediatric Detrusor Overactivity associated with a Neurologic Condition

Table 18 presents the most frequently reported adverse reactions in Study 191622-120, a double-blind, parallel-group study conducted in pediatric patients with detrusor overactivity associated with a neurologic condition. These patients were not adequately managed with at least one anticholinergic agent and were using clean intermittent catheterization at baseline [see *Clinical Studies (14.3)*]. The table below presents the most frequently reported adverse reactions during the 12 weeks following intradetrusor administration of BOTOX 200 Units.

Table 18: Adverse Reactions Reported by $\geq 3\%$ of BOTOX Treated Pediatric Patients within the First 12 Weeks after Intradetrusor Injection, Study 191622-120

Adverse Reactions	BOTOX 200 Unit (N=30)
Urinary tract infection	2 (7%)
Bacteriuria	6 (20%)
Leukocyturia	2 (7%)
Hematuria	1 (3%)

No change was observed in the overall safety profile with repeat dosing.

The most common adverse reactions in patients who received BOTOX 6 U/kg and less than a total dose of 200 U in Study 191622-120 were urinary tract infection (UTI), bacteriuria and hematuria.

Chronic Migraine

In double-blind, placebo-controlled chronic migraine efficacy trials (Study 1 and Study 2), the discontinuation rate was 12% in the BOTOX treated group and 10% in the placebo-treated group. Discontinuations due to an adverse event were 4% in the BOTOX group and 1% in the placebo group. The most frequent adverse events leading to discontinuation in the BOTOX group were neck pain, headache, worsening migraine, muscular weakness and eyelid ptosis.

The most frequently reported adverse reactions following injection of BOTOX for chronic migraine appear in Table 19.

Table 19: Adverse Reactions Reported by $\geq 2\%$ of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients in Two Chronic Migraine Double-Blind, Placebo-Controlled Clinical Trials

Adverse Reactions	BOTOX 155 Units-195 Units (N=687) %	Placebo (N=692) %
Nervous system disorders		
Headache	5	3
Migraine	4	3
Facial paresis	2	0
Eye disorders		
Eyelid ptosis	4	<1
Infections and Infestations		
Bronchitis	3	2
Musculoskeletal and connective tissue disorders		
Neck pain	9	3
Musculoskeletal stiffness	4	1
Muscular weakness	4	<1
Myalgia	3	1
Musculoskeletal pain	3	1
Muscle spasms	2	1
General disorders and administration site conditions		
Injection site pain	3	2
Vascular Disorders		
Hypertension	2	1

Other adverse reactions that occurred more frequently in the BOTOX group compared to the placebo group at a frequency less than 1% and potentially BOTOX related include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% of BOTOX treated patients in Study 1 and Study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Adult Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX for adult upper limb spasticity appear in Table 20.

Table 20: Adverse Reactions Reported by $\geq 2\%$ of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients in Adult Upper Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trials

Adverse Reactions	BOTOX 251 Units - 360 Units (N=115) %	BOTOX 150 Units - 250 Units (N=188) %	BOTOX <150 Units (N=54) %	Placebo (N=182) %
Gastrointestinal disorder				
Nausea	3	2	2	1
General disorders and administration site conditions				
Fatigue	3	2	2	0
Infections and infestations				
Bronchitis	3	2	0	1
Musculoskeletal and connective tissue disorders				
Pain in extremity	6	5	9	4
Muscular weakness	0	4	2	1

Twenty-two adult patients, enrolled in double-blind placebo controlled studies, received 400 Units or higher of BOTOX for treatment of upper limb spasticity. In addition, 44 adults received 400 Units of BOTOX or higher for four consecutive treatments over approximately one year for treatment of upper limb spasticity. The type and frequency of adverse reactions observed in patients treated with 400 Units of BOTOX were similar to those reported in patients treated for upper limb spasticity with 360 Units of BOTOX.

Adult Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX for adult lower limb spasticity appear in Table 21. Two hundred thirty-one patients enrolled in a double-blind placebo controlled study (Study 7) received 300 Units to 400 Units of BOTOX, and were compared with 233 patients who received placebo. Patients were followed for an average of 91 days after injection.

Table 21: Adverse Reactions Reported by $\geq 2\%$ of BOTOX Treated Patients and More Frequent than in Placebo-Treated Patients in Adult Lower Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 7)

Adverse Reactions	BOTOX (N=231) %	Placebo (N=233) %
Musculoskeletal and connective tissue disorders		
Arthralgia	3	1
Back pain	3	2
Myalgia	2	1
Infections and infestations		
Upper respiratory tract infection	2	1
General disorders and administration site conditions		
Injection site pain	2	1

Pediatric Upper Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric patients 2 to 17 years of age with upper limb spasticity appear in Table 22. In a double-blind, placebo-controlled trial (Study 1), 78 patients were treated with 3 Units/kg of BOTOX, and 77 patients received 6 Units/kg to a maximum dose of 200 Units of BOTOX, and were compared to 79 patients who received placebo [see *Clinical Studies (14.6)*]. Patients were followed for an average of 91 days after injection.

Table 22: Adverse Reactions Reported by $\geq 2\%$ of BOTOX 6 Units/kg Treated Patients and More Frequent than in Placebo-Treated Patients in Pediatric Upper Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 1)

Adverse Reactions	BOTOX 6 Units/kg (N=77) %	BOTOX 3 Units/kg (N=78) %	Placebo (N=79) %
Infections and infestations			
Upper respiratory tract infection*	17	10	9
General disorders and administration site conditions			
Injection site pain	4	3	1
Gastrointestinal disorders			
Nausea	4	0	0
Constipation	3	0	1
Respiratory, thoracic and mediastinal disorders			
Rhinorrhea	4	0	1
Nasal congestion	3	0	1
Nervous system disorders			
Seizure**	5	1	0

*Includes upper respiratory tract infection and viral upper respiratory tract infection

**Includes seizure and partial seizure

Pediatric Lower Limb Spasticity

The most frequently reported adverse reactions following injection of BOTOX in pediatric patients 2 to 17 years of age with lower limb spasticity appear in Table 23. In a double-blind, placebo-controlled trial (Study 2), 126 patients were treated with 4 Units/kg of BOTOX, and 128 patients received 8 Units/kg to a maximum dose of 300 Units of BOTOX, and were compared to 128 patients who received placebo [see *Clinical Studies (14.6)*]. Patients were followed for an average of 89 days after injection.

Table 23: Adverse Reactions Reported by $\geq 2\%$ of BOTOX 8 Units/kg Treated Patients and More Frequent than in Placebo-Treated Patients in Pediatric Lower Limb Spasticity Double-Blind, Placebo-Controlled Clinical Trial (Study 2)

Adverse Reactions	BOTOX 8 Units/kg (N=128) %	BOTOX 4 Units/kg (N=126) %	Placebo (N=128) %
General disorders and administration site conditions			
Injection site erythema	2	0	0
Injection site pain	2	2	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2	0	1
Injury, poisoning and procedural complications			
Ligament sprain	2	1	0
Skin abrasion	2	0	0
Metabolism and nutrition disorders			
Decreased appetite	2	0	0

Cervical Dystonia

In cervical dystonia patients evaluated for safety in double-blind and open-label studies following injection of BOTOX, the most frequently reported adverse reactions were dysphagia (19%), upper respiratory infection (12%), neck pain (11%), and headache (11%).

Other events reported in 2-10% of patients in any one study in decreasing order of incidence include: increased cough, flu syndrome, back pain, rhinitis, dizziness, hypertonia, soreness at injection site, asthenia, oral dryness, speech disorder, fever, nausea, and drowsiness. Stiffness, numbness, diplopia, ptosis, and dyspnea have been reported.

Dysphagia and symptomatic general weakness may be attributable to an extension of the pharmacology of BOTOX resulting from the spread of the toxin outside the injected muscles [see *Warnings and Precautions* (5.1, 5.6)].

The most common severe adverse reaction associated with the use of BOTOX injection in patients with cervical dystonia is dysphagia with about 20% of these cases also reporting dyspnea [see *Warnings and Precautions* (5.1, 5.6)]. Most dysphagia is reported as mild or moderate in severity. However, it may be associated with more severe signs and symptoms [see *Warnings and Precautions* (5.6)].

Additionally, reports in the literature include a case of a female patient who developed brachial plexopathy two days after injection of 120 Units of BOTOX for the treatment of cervical dystonia, and reports of dysphonia in patients who have been treated for cervical dystonia.

Primary Axillary Hyperhidrosis

The most frequently reported adverse reactions (3-10% of adult patients) following injection of BOTOX in double-blind studies included injection site pain and hemorrhage, non-axillary sweating, infection, pharyngitis, flu syndrome, headache, fever, neck or back pain, pruritus, and anxiety.

The data reflect 346 patients exposed to BOTOX 50 Units and 110 patients exposed to BOTOX 75 Units in each axilla.

Blepharospasm

In a study of blepharospasm patients who received an average dose per eye of 33 Units (injected at 3 to 5 sites) of the currently manufactured BOTOX, the most frequently reported adverse reactions were ptosis (21%), superficial punctate keratitis (6%), and eye dryness (6%).

Other events reported in prior clinical studies in decreasing order of incidence include: irritation, tearing, lagophthalmos, photophobia, ectropion, keratitis, diplopia, entropion, diffuse skin rash, and local swelling of the eyelid skin lasting for several days following eyelid injection.

In two cases of VII nerve disorder, reduced blinking from BOTOX injection of the orbicularis muscle led to serious corneal exposure, persistent epithelial defect, corneal ulceration and a case of corneal perforation. Focal facial paralysis, syncope, and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Strabismus

Extraocular muscles adjacent to the injection site can be affected, causing vertical deviation, especially with higher doses of BOTOX. The incidence rates of these adverse effects in 2058 adults who received a total of 3650 injections for horizontal strabismus was 17%.

The incidence of ptosis has been reported to be dependent on the location of the injected muscles, 1% after inferior rectus injections, 16% after horizontal rectus injections and 38% after superior rectus injections.

In a series of 5587 injections, retrobulbar hemorrhage occurred in 0.3% of cases.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to onabotulinumtoxinA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a long term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment sessions with the current formulation of BOTOX, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to BOTOX therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to BOTOX therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%), and no patients among 406 migraine patients with analyzed specimens developed the presence of neutralizing antibodies.

In one Phase 3 study and the open-label extension study in patients with pediatric lower limb spasticity, neutralizing antibodies developed in 2 of 264 patients (0.8%) treated with BOTOX for up to 5 treatment cycles. Both patients continued to experience clinical benefit following subsequent BOTOX treatments.

In overactive bladder patients with analyzed specimens from the two phase 3 studies and the open-label extension study, neutralizing antibodies developed in 0 of 954 patients (0.0%) while receiving BOTOX 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. Response to subsequent BOTOX treatment was not different following seroconversion in these three patients.

In detrusor overactivity associated with neurologic condition patients with analyzable specimens in the adult drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only BOTOX 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Following development of neutralizing antibodies in these 8 patients, 4 continued to experience clinical benefit, 2 did not experience clinical benefit, and the effect on the response to BOTOX in the remaining 2 patients is not known. In 99 pediatric patients who had a negative baseline result for binding antibodies or neutralizing antibodies and had at least one evaluable post-baseline value from one randomized double-blind study and one double-blind extension study, no patients developed neutralizing antibodies after receiving 50 Units to 200 Units of BOTOX.

The data reflect the patients whose test results were considered positive for neutralizing activity to BOTOX in a mouse protection assay or negative based on a screening ELISA assay or mouse protection assay.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the toxin. The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; brachial plexopathy; denervation/muscle atrophy; diarrhea; dry eye; eyelid edema (following periocular injection); hyperhidrosis; hypoacusis; hypoaesthesia; localized muscle twitching; malaise; Mephisto sign; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption; strabismus; tinnitus; and visual disturbances.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin [*see Warnings and Precautions (5.4, 5.6)*].

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

7 DRUG INTERACTIONS

7.1 Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

Co-administration of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

7.2 Anticholinergic Drugs

Use of anticholinergic drugs after administration of BOTOX may potentiate systemic anticholinergic effects.

7.3 Other Botulinum Neurotoxin Products

The effect of administering different botulinum neurotoxin 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.

7.4 Muscle Relaxants

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of BOTOX in pregnant women. In animal studies, administration of BOTOX during pregnancy resulted in adverse effects on fetal growth (decreased fetal weight and skeletal ossification) at clinically relevant doses, which were associated with maternal toxicity [*see Data*].

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively. The background risk of major birth defects and miscarriage for the indicated populations is unknown.

Data

Animal Data

When BOTOX (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately equal to the human dose of 400 Units, on a body weight basis (Units/kg).

When BOTOX was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the human dose of 400 Units, based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 2 times the human dose of 400 Units, based on Units/kg.

8.2 Lactation

Risk Summary

There are no data on the presence of BOTOX in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BOTOX and any potential adverse effects on the breastfed infant from BOTOX or from the underlying maternal conditions.

8.4 Pediatric Use

Detrusor Overactivity associated with a Neurologic Condition

The safety and effectiveness of BOTOX for detrusor overactivity associated with a neurologic condition have been established in pediatric patients 5 years of age and older who have an inadequate response to or are intolerant of anticholinergic medication. Use of BOTOX in this patient population is based on the results of a randomized, double-blind, parallel group trial in 113 pediatric patients 5 to 17 years of age (inclusive) with detrusor overactivity associated with a neurologic condition (Study 191622-120) and a long-term, multicenter, double-blind, long-term extension trial (Study 191622-121) [see *Clinical Studies* (14.3)]. The most common adverse reactions in this population were urinary tract infection, bacteriuria, hematuria, and leukocyturia [see *Adverse Reactions* (6.1)]. The safety and effectiveness of BOTOX have not been established in patients with NDO younger than 5 years of age.

Overactive Bladder

The safety and effectiveness of BOTOX for the treatment of overactive bladder have not been established in pediatric patients.

Efficacy was not demonstrated in a multicenter, randomized, double-blind, parallel-group, multiple-dose clinical study which was conducted to evaluate the efficacy and safety of BOTOX in pediatric patients aged 12 to 17 years with overactive bladder. Fifty-five patients who had an inadequate response to or were intolerant of at least one anticholinergic medication were treated with BOTOX. There was not a statistically significant difference in the mean change from baseline in the daily average frequency of daytime urinary incontinence episodes (primary efficacy endpoint) at week 12 post-treatment when a medium and high dose were each compared to a low dose of BOTOX. The adverse reactions in pediatric patients treated with BOTOX were comparable with the known safety profile in adults with overactive bladder.

Prophylaxis of Headaches in Chronic Migraine

Safety and effectiveness in patients below the age of 18 years have not been established.

In a 12-week, multicenter, double-blind, placebo-controlled clinical trial, 123 adolescent patients (ages 12 to below 18 years) with chronic migraine were randomized to receive BOTOX 74 Units, BOTOX 155 Units, or placebo, for one injection cycle. This trial did not establish the efficacy of BOTOX, compared with placebo, for the prophylaxis of headaches in adolescents with chronic migraine.

Spasticity

Safety and effectiveness have been established in pediatric patients 2 to 17 years of age [see *Warnings and Precautions* (5.1), *Adverse Reactions* (6.1), and *Clinical Studies* (14.6)]. The safety and effectiveness of BOTOX have been established by evidence from adequate and well-controlled studies of BOTOX in patients 2 to 17 years of age with upper and lower limb spasticity.

Safety and effectiveness in pediatric patients below the age of 2 years have not been established [see *Boxed Warning and Warnings and Precautions* (5.1)].

Axillary Hyperhidrosis

Safety and effectiveness in patients below the age of 18 years have not been established.

Cervical Dystonia

Safety and effectiveness in pediatric patients below the age of 16 years have not been established.

Blepharospasm and Strabismus

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Juvenile Animal Data

In a study in which juvenile rats received intramuscular injection of BOTOX (0, 8, 16, or 24 Units/kg) every other week from postnatal day 21 for 12 weeks, changes in bone size/geometry associated with decreased bone density and bone mass were observed at all doses, in association with limb disuse, decreased muscle contraction, and decreased body weight gain. Impairment of fertility and male reproductive organ histopathology (degeneration of seminiferous tubules of the testis) were observed at the mid and high doses. Bone and male reproductive organ effects showed evidence of reversibility after dosing cessation. The no-effect dose for adverse developmental effects in juvenile animals (8 Units/kg) is similar to the human dose (400 Units) on a body weight (kg) basis.

8.5 Geriatric Use

Of the 2145 adult patients in placebo-controlled clinical studies of BOTOX for the treatment of spasticity, 33.5% were 65 or older, and 7.7% were 75 years of age or older. No overall differences in safety were observed between elderly patients and adult patients younger than 65 years of age.

In clinical studies of BOTOX across other indications, no overall differences in safety were observed between elderly patients and younger adult patients, with the exception of Overactive Bladder (see below). Other reported clinical experience has not identified differences in responses between the elderly and younger adult patients, but greater sensitivity of some older individuals cannot be ruled out.

Overactive Bladder

Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% were 65 years of age or older, and 14.7% were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 24). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to adult patients younger than 65 years of age in these studies.

Table 24: Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-Controlled Treatment, Placebo-Controlled Clinical Trials in Patients with OAB

Adverse Reactions	<65 Years		65 to 74 Years		≥75 Years	
	BOTOX 100 Units (N=344)	Placebo (N=348)	BOTOX 100 Units (N=169)	Placebo (N=151)	BOTOX 100 Units (N=94)	Placebo (N=86)
	%	%	%	%	%	%
Urinary tract infection	21	7	30	13	38	19
Urinary retention	6	0.6	8	0	9	1

Observed effectiveness was comparable between these age groups in placebo-controlled clinical studies.

10 OVERDOSAGE

Excessive doses of BOTOX (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection [see *Boxed Warning and Warnings and Precautions (5.1, 5.6)*]. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm>.

11 DESCRIPTION

OnabotulinumtoxinA is a sterile, vacuum-dried purified botulinum toxin type A, produced from fermentation of Hall strain *Clostridium botulinum* type A, and intended for intramuscular, intradetrusor and intradermal use. It is purified from the culture solution by dialysis and a series of acid precipitations to a complex consisting of the neurotoxin, and several accessory proteins. The complex is dissolved in sterile sodium chloride solution containing Albumin Human and is sterile filtered (0.2 microns) prior to filling and vacuum-drying.

The primary release procedure for BOTOX uses a cell-based potency assay to determine the potency relative to a reference standard. The assay is specific to AbbVie's products BOTOX and BOTOX Cosmetic. One Unit of BOTOX corresponds to the calculated median intraperitoneal lethal dose (LD₅₀) in mice. Due to specific details of this assay such as the vehicle, dilution scheme, and laboratory protocols, Units of biological activity of BOTOX cannot be compared to nor converted into Units of any other botulinum toxin or any toxin assessed with any other specific assay method. The specific activity of BOTOX is approximately 20 Units/nanogram of neurotoxin protein complex.

Each vial of BOTOX (onabotulinumtoxinA) for injection contains either 100 Units of Clostridium botulinum type A neurotoxin complex, 0.5 mg of Albumin Human, and 0.9 mg of sodium chloride; or 200 Units of Clostridium botulinum type A neurotoxin complex, 1 mg of Albumin Human, and 1.8 mg of sodium chloride in a sterile, vacuum-dried form without a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

BOTOX blocks neuromuscular transmission by binding to acceptor sites on motor or autonomic nerve terminals, entering the nerve terminals, and inhibiting the release of acetylcholine. This inhibition occurs as the neurotoxin cleaves SNAP-25, a protein integral to the successful docking and release of acetylcholine from vesicles situated within nerve endings. When injected intramuscularly at therapeutic doses, BOTOX produces partial chemical denervation of the muscle resulting in a localized reduction in muscle activity. In addition, the muscle may atrophy, axonal sprouting may occur, and extrajunctional acetylcholine receptors may develop. There is evidence that reinnervation of the muscle may occur, thus slowly reversing muscle denervation produced by BOTOX.

When injected intradermally, BOTOX produces temporary chemical denervation of the sweat gland resulting in local reduction in sweating.

Following intradetrusor injection, BOTOX affects the efferent pathways of detrusor activity via inhibition of acetylcholine release.

12.3 Pharmacokinetics

Using currently available analytical technology, it is not possible to detect BOTOX in the peripheral blood following intramuscular injection at the recommended doses.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long term studies in animals have not been performed to evaluate the carcinogenic potential of BOTOX.

Mutagenesis

BOTOX was negative in a battery of in vitro (microbial reverse mutation assay, mammalian cell mutation assay, and chromosomal aberration assay) and in vivo (micronucleus assay) genetic toxicology assays.

Impairment of Fertility

In fertility studies of BOTOX (4, 8, or 16 Units/kg) in which either male or female rats were injected intramuscularly prior to mating and on the day of mating (3 doses, 2 weeks apart for males; 2 doses, 2 weeks apart for females) to untreated animals, reduced fertility was observed in males at the intermediate and high doses and in females at the high dose. The no-effect doses for reproductive toxicity (4 Units/kg in males, 8 Units/kg in females) are approximately equal to the human dose of 400 Units, on a body weight basis (Units/kg).

13.2 Animal Toxicology and/or Pharmacology

In a study to evaluate inadvertent peribladder administration, bladder stones were observed in 1 of 4 male monkeys that were injected with a total of 6.8 Units/kg divided into the prostatic urethra and proximal rectum (single administration). No bladder stones were observed in male or female monkeys following injection of up to 36 Units/kg (~12X the highest human bladder dose) directly to the bladder as either single or 4 repeat dose injections or in female rats for single injections up to 100 Units/kg (~33X the highest human bladder dose [200 Units], based on Units/kg).

14 CLINICAL STUDIES

14.1 Overactive Bladder (OAB)

Two double-blind, placebo-controlled, randomized, multi-center, 24-week clinical studies were conducted in patients with OAB with symptoms of urge urinary incontinence, urgency, and frequency (Studies OAB-1 and OAB-2). Patients needed to have at least 3 urinary urgency incontinence episodes and at least 24 micturitions in 3 days to enter the studies. A total of 1105 patients, whose symptoms had not been adequately managed with anticholinergic therapy (inadequate response or intolerable side effects), were randomized to receive either 100 Units of BOTOX (n=557), or placebo (n=548). Patients received 20 injections of study drug (5 Units of BOTOX or placebo) spaced approximately 1 cm apart into the detrusor muscle.

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of urinary incontinence episodes were observed for BOTOX 100 Units at the primary time point of week 12. Significant improvements compared to placebo were also observed for the secondary efficacy variables of daily frequency of micturition episodes and volume voided per micturition. These primary and secondary variables are shown in Table 25 and Table 26, and Figure 7 and Figure 8.

Table 25: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-1

	BOTOX 100 Units (N=278)	Placebo (N=272)	Treatment Difference	p-value
Daily Frequency of Urinary Incontinence Episodes^a				
Mean Baseline	5.5	5.1		
Mean Change* at Week 2	-2.6	-1.0	-1.6	
Mean Change* at Week 6	-2.8	-1.0	-1.8	
Mean Change* at Week 12**	-2.5	-0.9	-1.6 (-2.1, -1.2)	<0.001
Daily Frequency of Micturition Episodes^b				
Mean Baseline	12.0	11.2		
Mean Change [†] at Week 12**	-1.9	-0.9	-1.0 (-1.5, -0.6)	<0.001
Volume Voided per Micturition^b (mL)				
Mean Baseline	156	161		
Mean Change [†] at Week 12**	38	8	30 (17, 43)	<0.001

* Least squares (LS) mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. Last observation carried forward (LOCF) values were used to analyze the primary efficacy variable.

[†] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

** Primary timepoint

^a Primary variable

^b Secondary variable

Table 26: Baseline and Change from Baseline in Urinary Incontinence Episode Frequency, Micturition Episode Frequency and Volume Voided Per Micturition, Study OAB-2

	BOTOX 100 Units (N=275)	Placebo (N=269)	Treatment Difference	p-value
Daily Frequency of Urinary Incontinence Episodes^a				
Mean Baseline	5.5	5.7		
Mean Change* at Week 2	-2.7	-1.1	-1.6	
Mean Change* at Week 6	-3.1	-1.3	-1.8	
Mean Change* at Week 12**	-3.0	-1.1	-1.9 (-2.5, -1.4)	<0.001
Daily Frequency of Micturition Episodes^b				
Mean Baseline	12.0	11.8		
Mean Change [†] at Week 12**	-2.3	-0.6	-1.7 (-2.2, -1.3)	<0.001
Volume Voided per Micturition^b (mL)				
Mean Baseline	144	153		
Mean Change [†] at Week 12**	40	10	31 (20, 41)	<0.001

* LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and treatment group and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

[†] LS mean change, treatment difference and p-value are based on an ANCOVA model with baseline value as covariate and stratification factor, treatment group and investigator as factors.

** Primary timepoint

^a Primary variable

^b Secondary variable

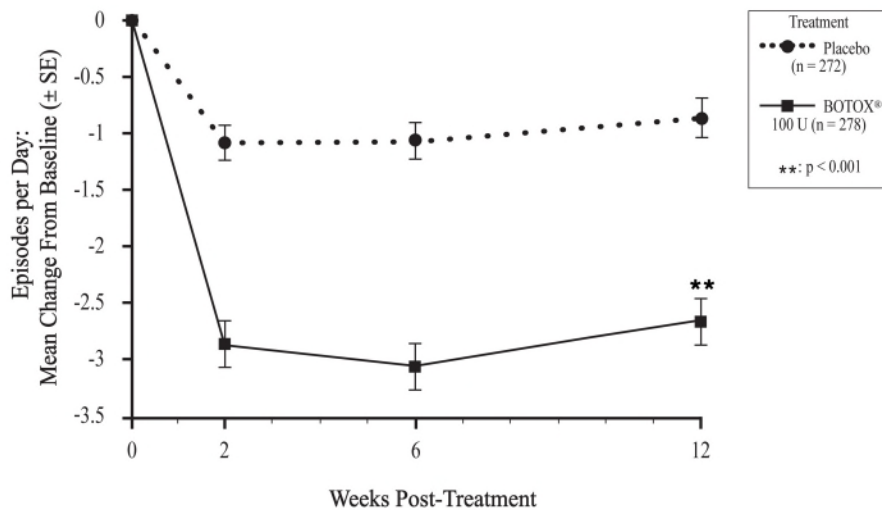
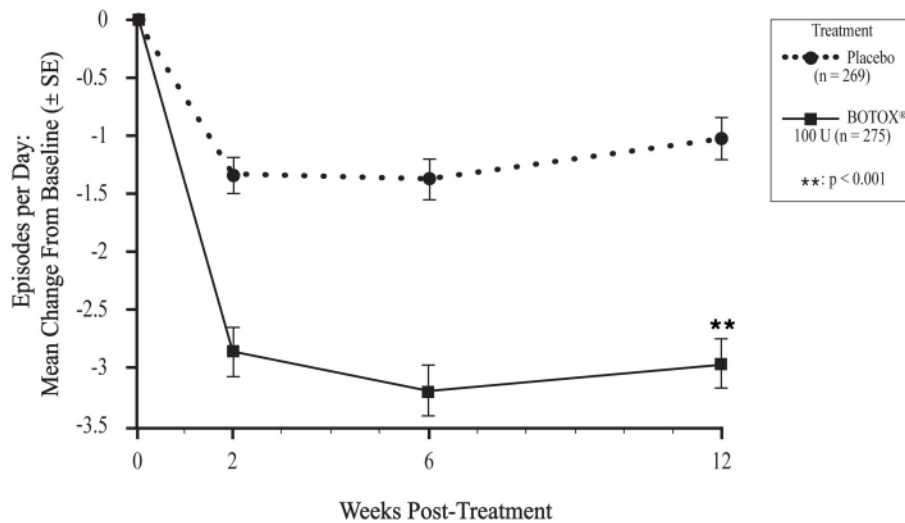
Figure 7: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes Following Intradetrusor Injection in Study OAB-1

Figure 8: Mean Change from Baseline in Daily Frequency of Urinary Incontinence Episodes Following Intradetrusor Injection in Study OAB-2



The median duration of response in Study OAB-1 and OAB-2, based on patient qualification for re-treatment, was 19-24 weeks for the BOTOX 100 Unit dose group compared to 13 weeks for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days.

14.2 Adult Detrusor Overactivity Associated with a Neurologic Condition

Two double-blind, placebo-controlled, randomized, multi-center clinical studies were conducted in patients with urinary incontinence due to detrusor overactivity associated with a neurologic condition who were either spontaneously voiding or using catheterization (Studies NDO-1 and NDO-2). A total of 691 spinal cord injury (T1 or below) or multiple sclerosis patients, who had an inadequate response to or were intolerant of at least one anticholinergic medication, were enrolled. These patients were randomized to receive either 200 Units of BOTOX (n=227), 300 Units of BOTOX (n=223), or placebo (n=241).

In both studies, significant improvements compared to placebo in the primary efficacy variable of change from baseline in weekly frequency of incontinence episodes were observed for BOTOX (200 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Table 27 and Table 28, and Figure 9 and Figure 10.

No additional benefit of BOTOX 300 Units over 200 Units was demonstrated.

Table 27: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) Study NDO-1

	BOTOX 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes^a				
N	134	146		
Mean Baseline	32.3	28.3		
Mean Change* at Week 2	-15.3	-10.0	-5.3	—
Mean Change* at Week 6**	-19.9	-10.6	-9.2	p<0.001
Mean Change* at Week 12	-19.8	-8.8	(-13.1, -5.3) -11.0	—
Maximum Cystometric Capacity^b (mL)				
N	123	129		
Mean Baseline	253.8	259.1		
Mean Change* at Week 6**	135.9	12.1	123.9 (89.1, 158.7)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction^b (cmH₂O)				
N	41	103		
Mean Baseline	63.1	57.4		
Mean Change* at Week 6**	-28.1	-3.7	-24.4	—

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

** Primary timepoint

^a Primary endpoint

^b Secondary endpoint

Table 28: Baseline and Change from Baseline in Weekly Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) in Study NDO-2

	BOTOX 200 Units	Placebo	Treatment Difference*	p-value*
Weekly Frequency of Urinary Incontinence Episodes^a				
N	91	91		
Mean Baseline	32.7	36.8		
Mean Change* at Week 2	-18.0	-7.9	-10.1	—
Mean Change* at Week 6**	-19.6	-10.8	-8.8	p=0.003
Mean Change* at Week 12	-19.6	-10.7	(-14.5, -3.0) -8.9	—
Maximum Cystometric Capacity^b (mL)				
N	88	85		
Mean Baseline	239.6	253.8		
Mean Change* at Week 6**	150.8	2.8	148.0 (101.8, 194.2)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction^b (cmH₂O)				
N	29	68		
Mean Baseline	65.6	43.7		
Mean Change* at Week 6**	-28.7	2.1	-30.7	—

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline weekly endpoint as covariate and treatment group, etiology at study entry (spinal cord injury or multiple sclerosis), concurrent anticholinergic therapy at screening, and investigator as factors. LOCF values were used to analyze the primary efficacy variable.

** Primary timepoint

^a Primary endpoint

^b Secondary endpoint

Figure 9: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-1

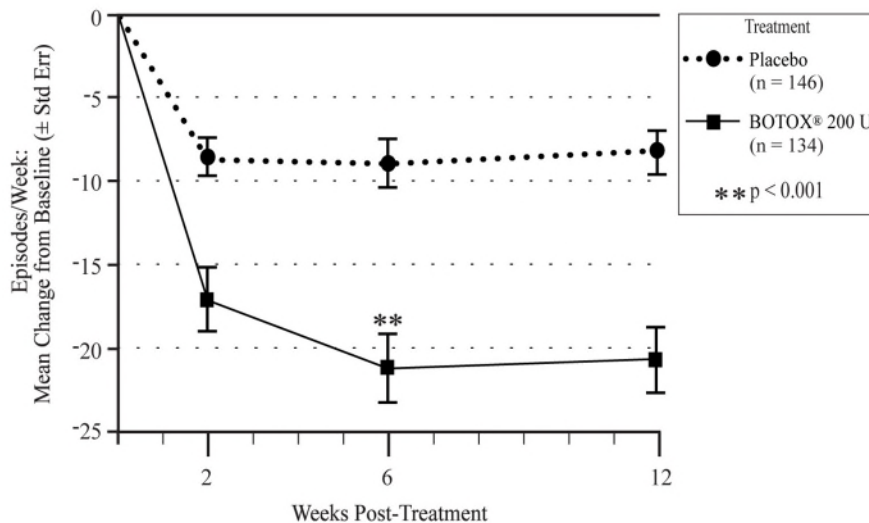
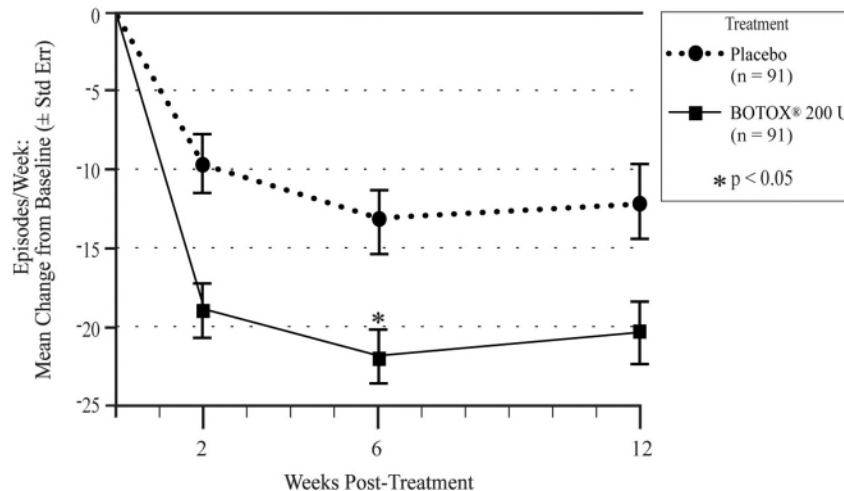


Figure 10: Mean Change from Baseline in Weekly Frequency of Urinary Incontinence Episodes During Treatment Cycle 1 in Study NDO-2



The median duration of response in study NDO-1 and NDO-2, based on patient qualification for re-treatment was 295-337 days (42-48 weeks) for the 200 Units dose group compared to 96-127 days (13-18 weeks) for placebo. Re-treatment was based on loss of effect on incontinence episode frequency (50% of effect in Study NDO-1; 70% of effect in Study NDO-2).

A placebo-controlled, double-blind randomized post-approval 52 week study (Study NDO-3) was conducted in MS patients with urinary incontinence due to neurogenic detrusor overactivity who were not adequately managed with at least one anticholinergic agent and not catheterizing at baseline. These patients were randomized to receive either 100 Units of BOTOX (n=66) or placebo (n=78).

Significant improvements compared to placebo in the primary efficacy variable of change from baseline in daily frequency of incontinence episodes were observed for BOTOX (100 Units) at the primary efficacy time point at week 6. Increases in maximum cystometric capacity and reductions in maximum detrusor pressure during the first involuntary detrusor contraction were also observed. These primary and secondary endpoints are shown in Table 29.

Table 29: Baseline and Change from Baseline in Daily Urinary Incontinence Episode Frequency, Maximum Cystometric Capacity and Maximum Detrusor Pressure during First Involuntary Detrusor Contraction (cmH₂O) in Study NDO-3

	BOTOX 100 Units	Placebo	Treatment Difference*	p-value*
Daily Frequency of Urinary Incontinence Episodes^a				
N	66	78		
Mean Baseline	4.2	4.3		
Mean Change* at Week 2	-2.9	-1.2	-1.7	—
Mean Change* at Week 6**	-3.4	-1.1	-2.3 (-3.0, -1.7)	p<0.001
Mean Change* at Week 12	-2.7	-1.0	-1.8	—
Maximum Cystometric Capacity^b (mL)				
N	62	72		
Mean Baseline	248.9	245.5		
Mean Change* at Week 6**	134.4	3.5	130.9 (94.8, 167.0)	p<0.001
Maximum Detrusor Pressure during First Involuntary Detrusor Contraction^b (cmH₂O)				
N	25	51		
Mean Baseline	42.4	39.0		
Mean Change* at Week 6**	-19.2	2.7	-21.9 (-37.5, -6.3)	

* LS mean change, treatment difference and p-value are based on an analysis using an ANCOVA model with baseline daily endpoint as covariate and treatment group and propensity score stratification as factors. LOCF values were used to analyze the primary efficacy variable.

** Primary timepoint

^a Primary endpoint

^b Secondary endpoint

The median duration of response in study NDO-3, based on patient qualification for re-treatment was 362 days (52 weeks) for the BOTOX 100 Units dose group compared to 88 days (13 weeks) for placebo. To qualify for re-treatment, at least 12 weeks must have passed since the prior treatment, post-void residual urine volume must have been less than 200 mL and patients must have reported at least 2 urinary incontinence episodes over 3 days with no more than 1 incontinence-free day.

14.3 Pediatric Detrusor Overactivity Associated with a Neurologic Condition

Study 191622-120 (NCT01852045) was a multicenter, randomized, double-blind, parallel-group clinical study conducted in patients 5 to 17 years of age with urinary incontinence due to detrusor overactivity associated with a neurologic condition and using clean intermittent catheterization. A total of 113 patients (including 99 with spinal dysraphism such as spina bifida, 13 with spinal cord injury and 1 with transverse myelitis) who had an inadequate response to or were intolerant of at least one anticholinergic medication were enrolled. The median age was 11 years (range: 5 to 17 years), 49% were female; 75% were White, 10% were Black. These patients were randomized to 50 Units, 100 Units or 200 Units, not to exceed 6 Units/kg body weight. Patients receiving less than the randomized dose due to the 6 Units/kg maximum, were assigned to the nearest dose group for analysis. The sample size for BOTOX 50 Units, 100 Units, and 200 Units were 38, 45 and 30, respectively. Prior to treatment administration, patients received anesthesia based on age and local site practice. One hundred and nine patients (97.3%) received general anesthesia or conscious sedation and 3 patients (2.7%) received local anesthesia.

The study results demonstrated within group improvements in the primary efficacy variable of change from baseline in daytime urinary incontinence episodes (normalized to 12 hours) at the primary efficacy time point (Week 6) for all 3 BOTOX treatment groups. Additional benefits were seen with BOTOX 200 Units for measures related to reducing maximum bladder pressure when compared to 50 Units. The decrease in maximum detrusor pressure (MDP) during the storage phase (MDP defined as the highest value in the Pdet channel during the storage phase [e.g., the greater of the following: the maximum Pdet during the highest amplitude IDC, the maximum Pdet during a terminal detrusor contraction, the Pdet at the end of filling, or the highest Pdet at any other time during the storage phase]) for BOTOX 200 Units at Week 6 was greater than the decrease observed for 50 Units. Within group improvements for the primary and secondary endpoints for the 200 Units dose group are shown in Table 30.

The efficacy of BOTOX 6 U/kg for pediatric patients with NDO weighing less than 34 kg was comparable to that of BOTOX 200 U.

Table 30: Baseline and Change from Baseline in Daily Daytime Frequency of Urinary Incontinence Episodes, Urine Volume at First Morning Catheterization, Maximum Detrusor Pressure during the Storage Phase (cmH₂O), and Maximum Cystometric Capacity (mL) in Study191622-120

	BOTOX 200 U N=30
Daily average frequency of daytime urinary incontinence episodes^a	
Mean Baseline	3.7
Mean Change* at Week 2 (95% CI)	-1.1 (-1.7, -0.6)
Mean Change* at Week 6** (95% CI)	-1.3 (-1.8, -0.9)
Mean Change* at Week 12 (95% CI)	-0.9 (-1.5, -0.4)
Urine Volume at First Morning Catheterization (mL)^b	
Mean Baseline	187.7
Mean Change* at Week 2 (95% CI)	63.2 (27.9, 98.6)
Mean Change* at Week 6** (95% CI)	87.5 (52.1, 122.8)
Mean Change* at Week 12 (95% CI)	45.2 (10.0, 80.5)
Maximum Detrusor Pressure (PdetMax) During the Storage Phase (cm H₂O)^b	
Mean Baseline	56.7
Mean Change* at Week 6** (95% CI)	-27.3 (-36.4, -18.2)
Maximum Cystometric Capacity (mL) (MCC)^b	
Mean Baseline	202.3
Mean Change* at Week 6** (95% CI)	63.6 (29.0, 98.1)

CI = Confidence Interval

* LSmean change and 95% CI are based on an ANCOVA model with baseline value as covariate and treatment group, age (< 12 years or ≥ 12 years), baseline daytime urinary incontinence episodes (≤ 6 or > 6) and anticholinergic therapy (yes/no) at baseline as factors.

** Primary timepoint

^a Primary endpoint^b Secondary endpoint

The median duration of response in this study, based on patient qualification for re-treatment was 207 days (30 weeks) for BOTOX 200 Units dose group. To qualify for re-treatment, patients must have reported at least 2 urinary incontinence episodes over 2 days and at least 12 weeks have passed from the prior bladder injection.

14.4 Chronic Migraine

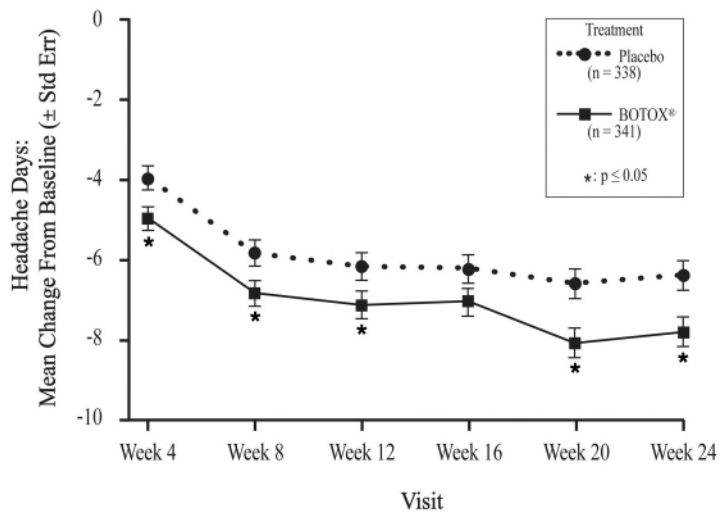
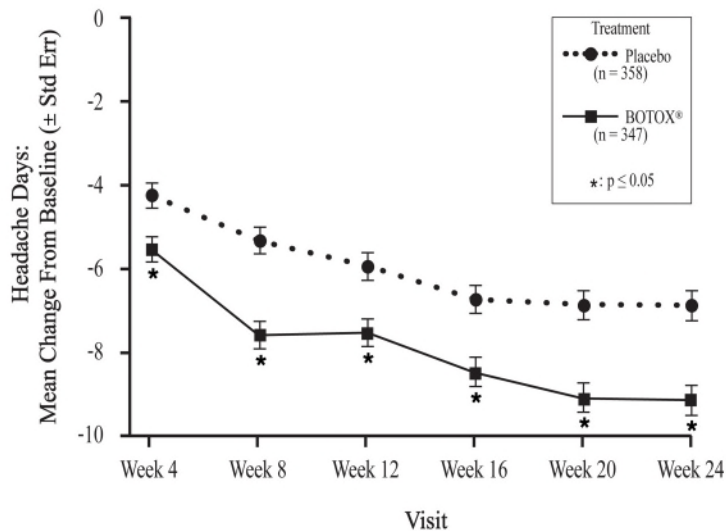
BOTOX was evaluated in two randomized, multi-center, 24-week, 2 injection cycle, placebo-controlled double-blind studies. Study 1 and Study 2 included chronic migraine adults who were not using any concurrent headache prophylaxis, and during a 28-day baseline period had ≥15 headache days lasting 4 hours or more, with ≥50% being migraine/probable migraine. In both studies, patients were randomized to receive placebo or 155 Units to 195 Units BOTOX injections every 12 weeks for the 2-cycle, double-blind phase. Patients were allowed to use acute headache treatments during the study. BOTOX treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy variables (see Table 31).

Table 31: Week 24 Key Efficacy Variables for Study 1 and Study 2

Efficacy per 28 days	Study 1		Study 2	
	BOTOX (N=341)	Placebo (N=338)	BOTOX (N=347)	Placebo (N=358)
Change from baseline in frequency of headache days	-7.8*	-6.4	-9.2*	-6.9
Change from baseline in total cumulative hours of headache on headache days	-107*	-70	-134*	-95

* Significantly different from placebo (p≤0.05)

Patients treated with BOTOX had a significantly greater mean decrease from baseline in the frequency of headache days at most timepoints from Week 4 to Week 24 in Study 1 (Figure 11), and all timepoints from Week 4 to Week 24 in Study 2 (Figure 12), compared to placebo-treated patients.

Figure 11: Mean Change from Baseline in Number of Headache Days for Study 1**Figure 12: Mean Change from Baseline in Number of Headache Days for Study 2**

14.5 Adult Spasticity

Adult Upper Limb Spasticity

The efficacy of BOTOX for the treatment of adult upper limb spasticity was evaluated in several randomized, multi-center, double-blind, placebo-controlled studies (Studies 1 through 6).

Study 1 included 126 adult patients (64 BOTOX and 62 placebo) with upper limb spasticity (Ashworth score of at least 3 for wrist flexor tone and at least 2 for finger flexor tone) who were at least 6 months post-stroke. BOTOX (a total dose of 200 Units to 240 Units) and placebo were injected intramuscularly (IM) into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and if necessary into the adductor pollicis and flexor pollicis longus (see Table 32). Use of an EMG/nerve stimulator was recommended to assist in proper muscle localization for injection. Patients were followed for 12 weeks.

Table 32: BOTOX Dose and Injection Sites in Study 1

Muscles Injected	Volume (mL)	BOTOX (Units)	Number of Injection Sites
Wrist			
Flexor Carpi Radialis	1	50	1
Flexor Carpi Ulnaris	1	50	1
Finger			
Flexor Digitorum Profundus	1	50	1
Flexor Digitorum Sublimis	1	50	1
Thumb			
Adductor Pollicis ^a	0.4	20	1
Flexor Pollicis Longus ^a	0.4	20	1

^a Injected only if spasticity is present in this muscle

The primary efficacy variable was wrist flexors muscle tone at week 6, as measured by the Ashworth score. The Ashworth Scale is a 5-point scale with grades of 0 [no increase in muscle tone] to 4 [limb rigid in flexion or extension]. It is a clinical measure of the force required to move an extremity around a joint, with a reduction in score clinically representing a reduction in the force needed to move a joint (i.e., improvement in spasticity).

Key secondary endpoints included Physician Global Assessment, finger flexors muscle tone, and thumb flexors tone at Week 6. The Physician Global Assessment evaluated the response to treatment in terms of how the patient was doing in his/her life using a scale from -4 = very marked worsening to +4 = very marked improvement. Study 1 results on the primary endpoint and the key secondary endpoints are shown in Table 33.

Table 33: Primary and Key Secondary Endpoints by Muscle Group at Week 6 in Study 1

	BOTOX (N=64)	Placebo (N=62)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale^{†a}	-2.0*	0.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale^{††b}	-1.0*	0.0
Median Change from Baseline in Thumb Flexor Muscle Tone on the Ashworth Scale^{††c}	-1.0	-1.0
Median Physician Global Assessment of Response to Treatment^{††}	2.0*	0.0

[†] Primary endpoint at Week 6

^{††} Secondary endpoints at Week 6

* Significantly different from placebo ($p \leq 0.05$)

^a BOTOX injected into both the flexor carpi radialis and ulnaris muscles

^b BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles

^c BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 2 compared 3 doses of BOTOX with placebo and included 91 adult patients [BOTOX 360 Units (N=21), BOTOX 180 Units (N=23), BOTOX 90 Units (N=21), and placebo (N=26)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 34).

Table 34: BOTOX Dose and Injection Sites in Study 2 and Study 3

Muscles Injected	Total Dose			Volume (mL) per site	Injection Sites (n)
	BOTOX low dose (90 Units)	BOTOX mid dose (180 Units)	BOTOX high dose (360 Units)		
Wrist					
Flexor Carpi Ulnaris	10 Units	20 Units	40 Units	0.4	1
Flexor Carpi Radialis	15 Units	30 Units	60 Units	0.6	1
Finger					
Flexor Digitorum Profundus	7.5 Units	15 Units	30 Units	0.3	1
Flexor Digitorum Sublimis	7.5 Units	15 Units	30 Units	0.3	1
Elbow					
Biceps Brachii	50 Units	100 Units	200 Units	0.5	4

The primary efficacy variable in Study 2 was the wrist flexor tone at Week 6 as measured by the expanded Ashworth Scale. The expanded Ashworth Scale uses the same scoring system as the Ashworth Scale, but allows for half-point increments.

Key secondary endpoints in Study 2 included Physician Global Assessment, finger flexors muscle tone, and elbow flexors muscle tone at Week 6. Study 2 results on the primary endpoint and the key secondary endpoints at Week 6 are shown in Table 35.

Table 35: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 6 in Study 2

	BOTOX low dose (90 Units) (N=21)	BOTOX mid dose (180 Units) (N=23)	BOTOX high dose (360 Units) (N=21)	Placebo (N=26)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale^{†b}	-1.5*	-1.0*	-1.5*	-1.0
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale^{††c}	-0.5	-0.5	-1.0	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale^{††d}	-0.5	-1.0*	-0.5 ^a	-0.5
Median Physician Global Assessment of Response to Treatment	1.0*	1.0*	1.0*	0.0

[†] Primary endpoint at Week 6

^{††} Secondary endpoints at Week 6

* Significantly different from placebo ($p \leq 0.05$)

^a $p=0.053$

^b Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles

^c Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles

^d Dose of BOTOX injected into biceps brachii muscle

Study 3 compared 3 doses of BOTOX with placebo and enrolled 88 adult patients [BOTOX 360 Units (N=23), BOTOX 180 Units (N=23), BOTOX 90 Units (N=23), and placebo (N=19)] with upper limb spasticity (expanded Ashworth score of at least 2 for elbow flexor tone and at least 3 for wrist flexor tone and/or finger flexor tone) who were at least 6 weeks post-stroke. BOTOX and placebo were injected with EMG guidance into the flexor digitorum profundus, flexor digitorum sublimis, flexor carpi radialis, flexor carpi ulnaris, and biceps brachii (see Table 34).

The primary efficacy variable in Study 3 was wrist and elbow flexor tone as measured by the expanded Ashworth score. A key secondary endpoint was assessment of finger flexors muscle tone. Study 3 results on the primary endpoint at Week 4 are shown in Table 36.

Table 36: Primary and Key Secondary Endpoints by Muscle Group and BOTOX Dose at Week 4 in Study 3

	BOTOX low dose (90 Units) (N=23)	BOTOX mid dose (180 Units) (N=21)	BOTOX high dose (360 Units) (N=22)	Placebo (N=19)
Median Change from Baseline in Wrist Flexor Muscle Tone on the Ashworth Scale^{†b}	-1.0	-1.0	-1.5*	-0.5
Median Change from Baseline in Finger Flexor Muscle Tone on the Ashworth Scale^{††c}	-1.0	-1.0	-1.0*	-0.5
Median Change from Baseline in Elbow Flexor Muscle Tone on the Ashworth Scale^{†d}	-0.5	-0.5	-1.0*	-0.5

† Primary endpoint at Week 4

†† Secondary endpoints at Week 4

* Significantly different from placebo ($p \leq 0.05$)^b Total dose of BOTOX injected into both the flexor carpi radialis and ulnaris muscles^c Total dose of BOTOX injected into the flexor digitorum profundus and flexor digitorum sublimis muscles^d Dose of BOTOX injected into biceps brachii muscle

Study 4 (NCT01153815) included 170 adult patients (87 BOTOX and 83 placebo) with upper limb spasticity who were at least 6 months post-stroke. In Study 4, patients received 20 Units of BOTOX into the adductor pollicis and flexor pollicis longus (total BOTOX dose = 40 Units in thumb muscles) or placebo (see Table 37). Study 5 (NCT00460564) included 109 patients with upper limb spasticity who were at least 6 months post-stroke. In Study 5, adult patients received 15 Units (low dose) or 20 Units (high dose) of BOTOX into the adductor pollicis and flexor pollicis longus under EMG guidance (total BOTOX low dose = 30 Units, total BOTOX high dose = 40 Units), or placebo (see Table 37). The duration of follow-up in Study 4 and Study 5 was 12 weeks.

Table 37: BOTOX Dose and Injection Sites in Studies 4 and 5

Muscles Injected	Study 4		Study 5				Number of Injection Sites for Studies 4 and 5
	BOTOX (Units)	Volume (mL)	BOTOX low dose (Units)	BOTOX high dose (Units)	Volume low dose (mL)	Volume high dose (mL)	
Thumb							
Adductor Pollicis	20	0.4	15	20	0.3	0.4	1
Flexor Pollicis Longus	20	0.4	15	20	0.3	0.4	1

The results of Study 4 for the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale (MAS) and overall treatment response by Physician Global Assessment at week 6 are presented in Table 38. The MAS uses a similar scoring system as the Ashworth Scale.

Table 38: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 4

	BOTOX (N=66)	Placebo (N=57)
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale^{††a}	-1.0*	0.0
Median Physician Global Assessment of Response to Treatment^{††}	2.0*	0.0

†† Secondary endpoints at Week 6

* Significantly different from placebo ($p \leq 0.001$)^a BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

In Study 5, the results of the change from Baseline to Week 6 in thumb flexor tone measured by modified Ashworth Scale and Clinical Global Impression (CGI) of functional assessment scale assessed by the physician using an 11-point Numeric Rating Scale [-5 worst possible function to +5 best possible function] are presented in Table 39.

Table 39: Efficacy Endpoints for Thumb Flexors at Week 6 in Study 5

	BOTOX low dose (30 Units) (N=14)	Placebo low dose (N=9)	BOTOX high dose (40 Units) (N=43)	Placebo high dose (N=23)
Median Change from Baseline in Thumb Flexor Muscle Tone on the modified Ashworth Scale^{†††a}	-1.0	-1.0	-0.5*	0.0
Median Change from Baseline in Clinical Global Impression Score by Physician^{††}	1.0	0.0	2.0*	0.0

^{††} Secondary endpoint at Week 6

^{†††} Other endpoint at Week 6

* Significantly different from placebo ($p \leq 0.010$)

^a BOTOX injected into the adductor pollicis and flexor pollicis longus muscles

Study 6 (NCT03261167) enrolled 124 post-stroke adult patients with upper limb spasticity. In Study 6, 61 patients received 160 Units BOTOX divided among 3 elbow flexors (biceps brachii, brachioradialis, and brachialis) and 63 patients received placebo (see Table 40). EMG, nerve stimulation, or ultrasound techniques were recommended to assist in proper muscle localization for injections. The duration of follow-up was 12 weeks.

Table 40: BOTOX Dose and Injection Sites in Study 6

Muscles Injected	BOTOX 160 U (Units)	Volume (mL)	Number of Injection Sites
Elbow			
Biceps Brachii	70	1.4	2
Brachioradialis	45	0.9	1
Brachialis	45	0.9	1

The change from baseline in elbow flexor tone measured by modified Ashworth Scale at Week 6 is presented in Table 41.

Table 41: Primary Efficacy Endpoint Results for Elbow Flexors at Week 6 in Study 6

	BOTOX 160 U (N=61)	Placebo (N=63)
Mean Change from Baseline in Elbow Flexor Muscle Tone on the modified Ashworth Scale at Week 6	-1.09*	-0.71

*nominal p value < 0.05

Adult Lower Limb Spasticity

The efficacy and safety of BOTOX for the treatment of adult lower limb spasticity was evaluated in Study 7, a randomized, multi-center, double-blind, placebo-controlled study. Study 7 included 468 post-stroke adult patients (233 BOTOX and 235 placebo) with ankle spasticity (modified Ashworth Scale ankle score of at least 3) who were at least 3 months post-stroke. A total dose of 300 Units of BOTOX or placebo were injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior, with optional injection into the flexor hallucis longus, flexor digitorum longus, flexor digitorum brevis, extensor hallucis, and rectus femoris (see Table 42) with up to an additional 100 Units (400 Units total dose). The use of electromyographic guidance or nerve stimulation was required to assist in proper muscle localization for injections. Patients were followed for 12 weeks.

Table 42: BOTOX Dose and Injection Sites in Study 7

Muscles Injected	BOTOX (Units)	Number of Injection Sites
Mandatory Ankle Muscles		
Gastrocnemius (medial head)	75	3
Gastrocnemius (lateral head)	75	3
Soleus	75	3
Tibialis Posterior	75	3
Optional Muscles		
Flexor Hallucis Longus	50	2
Flexor Digitorum Longus	50	2
Flexor Digitorum Brevis	25	1
Extensor Hallucis	25	1
Rectus Femoris	100	4

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Physician Global Assessment of Response (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale from -4=very marked worsening to +4=very marked improvement.

Statistically significant between-group differences for BOTOX over placebo were demonstrated for the co-primary efficacy measures of MAS and CGI (see Table 43).

Table 43: Co-Primary Efficacy Endpoints Results in Study 7 (Intent-To-Treat Population)

	BOTOX 300 to 400 Units (N=233)	Placebo (N=235)
Mean Change from Baseline in Ankle Plantar Flexors on the modified Ashworth Scale		
Week 4 and 6 Average	-0.8*	-0.6
Mean Clinical Global Impression Score by Investigator		
Week 4 and 6 Average	0.9*	0.7

* Significantly different from placebo ($p < 0.05$)

Compared to placebo, significant improvements in MAS change from baseline for ankle plantar flexors (see Figure 13) and CGI (see Figure 14) were observed at Week 2, Week 4, and Week 6 for patients treated with BOTOX.

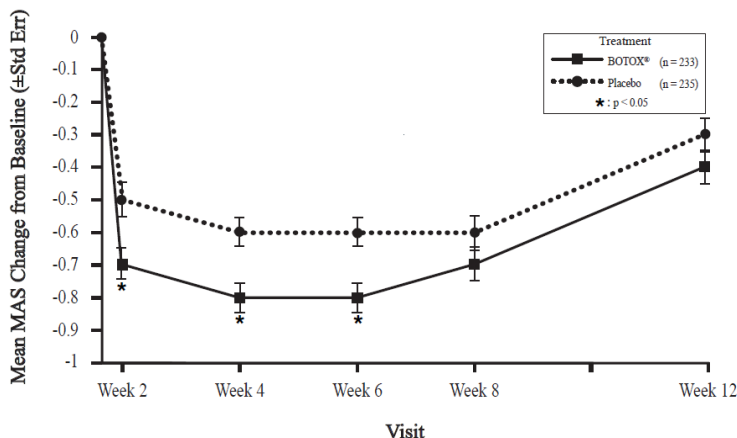
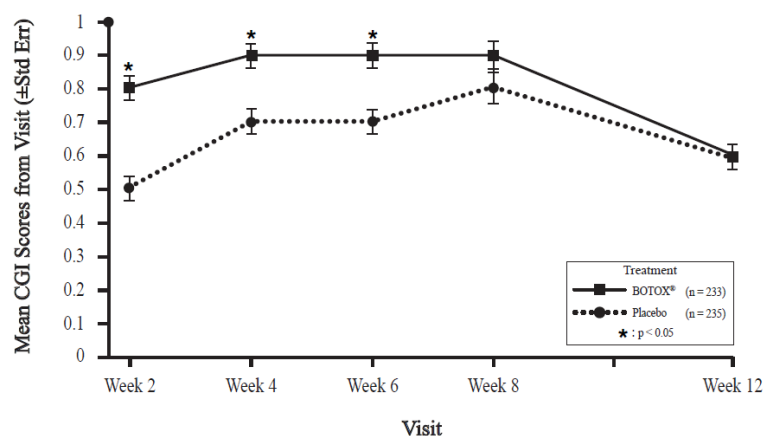
Figure 13: Modified Ashworth Scale Ankle Score for Study 7 – Mean Change from Baseline by Visit

Figure 14: Clinical Global Impression by Physician for Study 7 – Mean Scores by Visit

14.6 Pediatric Spasticity

Pediatric Upper Limb Spasticity

The efficacy and safety of BOTOX for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age was evaluated in Study 1 (NCT01603602), a randomized, multi-center, double-blind, placebo-controlled study. Study 1 included 234 pediatric patients (78 BOTOX 3 Units/kg, 77 BOTOX 6 Units/kg, and 79 placebo) with upper limb spasticity (modified Ashworth Scale elbow or wrist score of at least 2) because of cerebral palsy or stroke. A total dose of 3 Units/kg BOTOX (maximum 100 Units), 6 Units/kg BOTOX (maximum 200 Units), or placebo was injected intramuscularly and divided between the elbow or wrist and finger muscles (see Table 44). Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection.

Table 44: BOTOX Dose and Injection Sites in Study 1

Muscles Injected	BOTOX 3 Units/kg* (maximum Units per muscle)	BOTOX 6 Units/kg** (maximum Units per muscle)	Number of Injection Sites
Elbow Flexor Muscles			
Biceps	1.5 Units/kg (50 Units)	3 Units/kg (100 Units)	4
Brachialis	1 Unit/kg (30 Units)	2 Units/kg (60 Units)	2
Brachioradialis	0.5 Units/kg (20 Units)	1 Unit/kg (40 Units)	2
Wrist and Finger Muscles			
Flexor carpi radialis	1 Unit/kg (25 Units)	2 Units/kg (50 Units)	2
Flexor carpi ulnaris	1 Unit/kg (25 Units)	2 Units/kg (50 Units)	2
Flexor digitorum profundus	0.5 Units/kg (25 Units)	1 Unit/kg (50 Units)	2
Flexor digitorum sublimis	0.5 Units/kg (25 Units)	1 Unit/kg (50 Units)	2

* Did not exceed a total dose of 100 Units

** Did not exceed a total dose of 200 Units

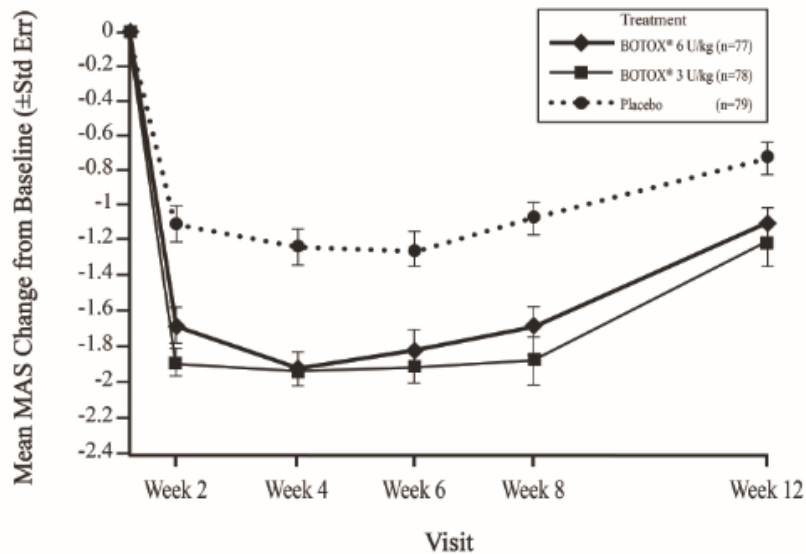
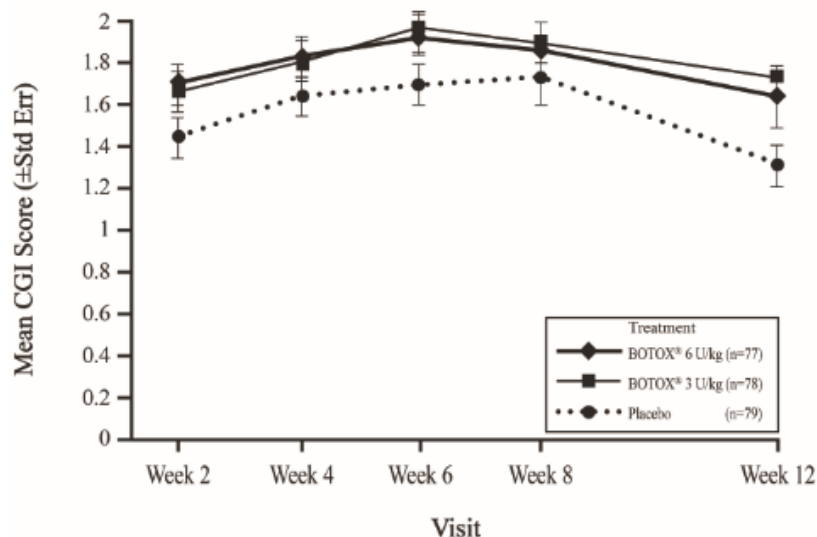
The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) principal muscle group score (elbow or wrist) at Week 4 and Week 6, and the average of the Clinical Global Impression of Overall Change by Physician (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4=very marked worsening to +4=very marked improvement).

Compared to placebo, significant improvements in MAS change from baseline were observed at all timepoints for BOTOX-treated patients (see Table 45, Figure 15 and Figure 16). Although CGI scores numerically favored BOTOX over placebo, the difference was not statistically significant.

Table 45: Co-Primary Efficacy Endpoints Results in Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population)

	BOTOX 3 Units/kg (N=78)	BOTOX 6 Units/kg (N=77)	Placebo (N=79)
Mean Change from Baseline in Principal Muscle Group (Elbow or Wrist) on the modified Ashworth Scale			
Week 4 and 6 Average	-1.92*	-1.87*	-1.21
Mean Clinical Global Impression Score			
Week 4 and 6 Average	1.88	1.87	1.66

*Nominal p value <0.05

Figure 15: Modified Ashworth Scale Score for Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population) – Mean Change from Baseline by Visit**Figure 16: Clinical Global Impression of Overall Change for Study 1 (Pediatric Upper Limb Spasticity, Modified Intent-To-Treat Population) – Mean Scores by Visit**

The efficacy and safety of BOTOX for the treatment of lower limb spasticity in pediatric patients 2 to 17 years of age was evaluated in Study 2 (NCT01603628), a randomized, multi-center, double-blind, placebo-controlled study. Study 2 included 381 pediatric patients (125 BOTOX 4 Units/kg, 127 BOTOX 8 Units/kg, and 129 placebo) with lower limb spasticity (modified Ashworth Scale ankle score of at least 2) because of cerebral palsy. A total dose of 4 Units/kg BOTOX (maximum 150 Units), 8 Units/kg BOTOX (maximum 300 Units), or placebo was injected intramuscularly and divided between the gastrocnemius, soleus, and tibialis posterior (see Table 46). Electromyographic guidance, nerve stimulation, or ultrasound techniques were used to assist in muscle localization for injections. Patients were followed for 12 weeks after injection.

Table 46: BOTOX Dose and Injection Sites in Study 2

Muscles Injected	BOTOX 4 Units/kg* (maximum Units per muscle)	BOTOX 8 Units/kg** (maximum Units per muscle)	Number of Injection Sites
Mandatory Ankle Muscles			
Gastrocnemius medial head	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Gastrocnemius lateral head	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Soleus	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2
Tibialis Posterior	1 Unit/kg (37.5 Units)	2 Units/kg (75 Units)	2

* did not exceed a total dose of 150 Units

** did not exceed a total dose of 300 Units

The co-primary endpoints were the average of the change from baseline in modified Ashworth Scale (MAS) ankle score at Week 4 and Week 6, and the average of the Clinical Global Impression of Overall Change by Physician (CGI) at Week 4 and Week 6. The CGI evaluated the response to treatment in terms of how the patient was doing in his/her life using a 9-point scale (-4=very marked worsening to +4=very marked improvement).

Statistically significant differences between BOTOX and placebo were demonstrated for the MAS and CGI for the 8 Units/kg dose only (see Table 47).

Table 47: Co-Primary Efficacy Endpoints Results in Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population)

	BOTOX 4 Units/kg (N = 125)	BOTOX 8 Units/kg (N=127)	Placebo (N=129)
Mean Change from Baseline in Plantar Flexors on the modified Ashworth Scale			
Week 4 and 6 Average	-1.01**	-1.06*	-0.80
Mean Clinical Global Impression Score			
Week 4 and 6 Average	1.49	1.65*	1.36

* Significantly different from placebo (p<0.05)

** Nominal p value <0.05

Compared to placebo, improvements in mean change from baseline for the MAS, and mean CGI score for lower limb spasticity were observed at timepoints up to Week 12 for BOTOX-treated patients (see Figure 17 and Figure 18).

Figure 17: Modified Ashworth Scale Ankle Score for Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population) – Mean Change from Baseline by Visit

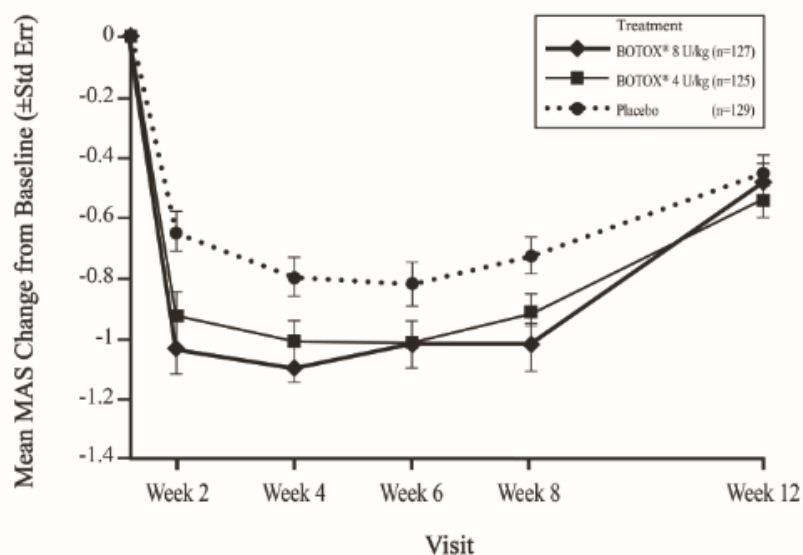
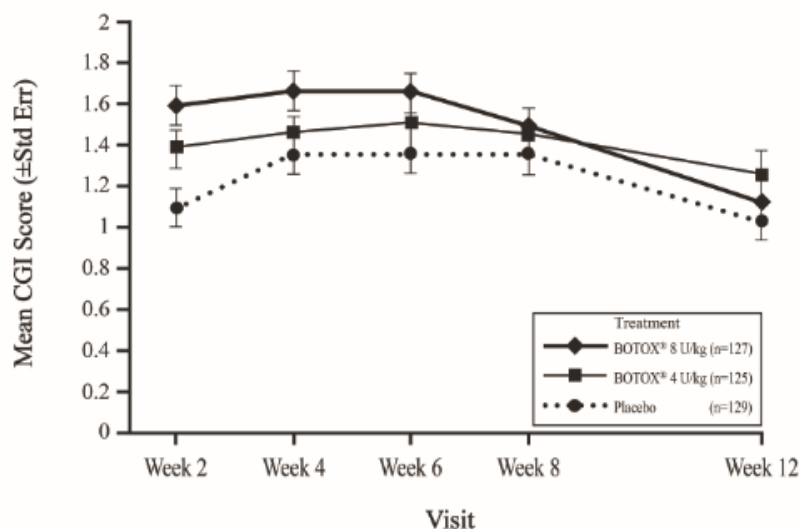


Figure 18: Clinical Global Impression of Overall Change for Study 2 (Pediatric Lower Limb Spasticity, Modified Intent-To-Treat Population) – Mean Scores by Visit



14.7 Cervical Dystonia

A randomized, multi-center, double-blind, placebo-controlled study of the treatment of cervical dystonia was conducted. This study enrolled adult patients with cervical dystonia and a history of having received BOTOX in an open label manner with perceived good response and tolerable side effects. Patients were excluded if they had previously received surgical or other denervation treatment for their symptoms or had a known history of neuromuscular disorder. Subjects participated in an open label enrichment period where they received their previously employed dose of BOTOX. Only patients who were again perceived as showing a response were advanced to the randomized evaluation period. The muscles in which the blinded study agent injections were to be administered were determined on an individual patient basis.

There were 214 subjects evaluated for the open label period, of which 170 progressed into the randomized, blinded treatment period (88 in the BOTOX group, 82 in the placebo group). Patient evaluations continued for at least 10 weeks post-injection. The primary outcome for the study was a dual endpoint, requiring evidence of both a change in the Cervical Dystonia Severity Scale (CDSS) and an increase in the percentage of patients showing any improvement on the Physician Global Assessment Scale at 6 weeks after the injection session. The CDSS quantifies the severity of abnormal head positioning and was newly devised for this study. CDSS allots 1 point for each 5 degrees (or part thereof) of head deviation in each of the three planes of head movement (range of scores up to theoretical maximum of 54). The Physician Global Assessment Scale is a 9 category scale scoring the physician's evaluation of the patients' status compared to baseline, ranging from -4 to +4 (very marked worsening to complete improvement), with 0 indicating no

change from baseline and +1 slight improvement. Pain is also an important symptom of cervical dystonia and was evaluated by separate assessments of pain frequency and severity on scales of 0 (no pain) to 4 (constant in frequency or extremely severe in intensity). Study results on the primary endpoints and the pain-related secondary endpoints are shown in Table 48.

Table 48: Efficacy Outcomes of the Phase 3 Cervical Dystonia Study (Group Means)

	Placebo (N=82)	BOTOX (N=88)	95% CI on Difference
Baseline CDSS	9.3	9.2	
Change in CDSS at Week 6	-0.3	-1.3	(-2.3, 0.3) ^[a,b]
% Patients with Any Improvement on Physician Global Assessment	31%	51%	(5%, 34%) ^[a]
Pain Intensity Baseline	1.8	1.8	
Change in Pain Intensity at Week 6	-0.1	-0.4	(-0.7, -0.2) ^[c]
Pain Frequency Baseline	1.9	1.8	
Change in Pain Frequency at Week 6	-0.0	-0.3	(-0.5, -0.0) ^[c]

^[a] Confidence intervals are constructed from the analysis of covariance table with treatment and investigational site as main effects, and baseline CDSS as a covariate.

^[b] These values represent the prospectively planned method for missing data imputation and statistical test. Sensitivity analyses indicated that the 95% confidence interval excluded the value of no difference between groups and the p-value was less than 0.05. These analyses included several alternative missing data imputation methods and non-parametric statistical tests.

^[c] Confidence intervals are based on the t-distribution.

Exploratory analyses of this study suggested that the majority of patients who had shown a beneficial response by week 6 had returned to their baseline status by 3 months after treatment. Exploratory analyses of subsets by patient sex and age suggest that both sexes receive benefit, although female patients may receive somewhat greater amounts than male patients. There is a consistent treatment-associated effect between subsets greater than and less than age 65. There were too few non-Caucasian patients enrolled to draw any conclusions regarding relative efficacy in racial subsets.

In this study the median total BOTOX dose in patients randomized to receive BOTOX (N=88) was 236 Units, with 25th to 75th percentile ranges of 198 Units to 300 Units. Of these 88 patients, most received injections to 3 or 4 muscles; 38 received injections to 3 muscles, 28 to 4 muscles, 5 to 5 muscles, and 5 to 2 muscles. The dose was divided amongst the affected muscles in quantities shown in Table 49. The total dose and muscles selected were tailored to meet individual patient needs.

Table 49: Number of Patients Treated per Muscle and Fraction of Total Dose Injected into Involved Muscles

Muscle	Number of Patients Treated in this Muscle (N=88)	Mean % Dose per Muscle	Mid-Range of % Dose per Muscle*
Splenius capitis/cervicis	83	38	25-50
Sternocleidomastoid	77	25	17-31
Levator scapulae	52	20	16-25
Trapezius	49	29	18-33
Semispinalis	16	21	13-25
Scalene	15	15	6-21
Longissimus	8	29	17-41

* The mid-range of dose is calculated as the 25th to 75th percentiles.

There were several randomized studies conducted prior to the double-blind, placebo-controlled study, which were supportive but not adequately designed to assess or quantitatively estimate the efficacy of BOTOX.

14.8 Primary Axillary Hyperhidrosis

The efficacy and safety of BOTOX for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multi-center, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = “underarm sweating is never noticeable and never interferes with my daily activities”; to 4 = “underarm sweating is intolerable and always interferes with my daily activities”. A total of 322 patients were randomized in a 1:1:1

ratio to treatment in both axillae with either 50 Units of BOTOX, 75 Units of BOTOX, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46% to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102 mg, 123 mg, and 114 mg for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both BOTOX groups than in the placebo group ($p < 0.001$), but was not significantly different between the two BOTOX doses (see Table 50).

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in BOTOX treated patients with either dose was 201 days. Among those who received a second BOTOX injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of BOTOX ($n=242$) or placebo ($n=78$). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the BOTOX group and 36% (28/78) in the placebo group, $p < 0.001$. The difference in percentage of responders between BOTOX and placebo was 55% (95% CI=43.3, 65.9).

Table 50: Study 1 - Study Outcomes

Treatment Response	BOTOX 50 Units (N=104)	BOTOX 75 Units (N=110)	Placebo (N=108)	BOTOX 50-placebo (95% CI)	BOTOX 75-placebo (95% CI)
HDSS Score change ≥ 2 (n)^a	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat production % (n)	81% (84)	86% (94)	41% (44)	40% (28.1, 52.0)	45% (33.3, 56.1)

^a Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

14.9 Blepharospasm

Botulinum toxin has been investigated for use in patients with blepharospasm in several studies. In an open label, historically controlled study, 27 patients with essential blepharospasm were injected with 2 Units of BOTOX at each of six sites on each side. Twenty-five of the 27 patients treated with botulinum toxin reported improvement within 48 hours. One patient was controlled with a higher dosage at 13 weeks post initial injection and one patient reported mild improvement but remained functionally impaired.

In another study, 12 patients with blepharospasm were evaluated in a double-blind, placebo-controlled study. Patients receiving botulinum toxin ($n=8$) improved compared with the placebo group ($n=4$). The effects of the treatment lasted a mean of 12 weeks.

One thousand six hundred eighty-four patients with blepharospasm who were evaluated in an open label trial showed clinical improvement as evaluated by measured eyelid force and clinically observed intensity of lid spasm, lasting an average of 12 weeks prior to the need for re-treatment.

14.10 Strabismus

Six hundred seventy-seven patients with strabismus treated with one or more injections of BOTOX were evaluated in an open label trial. Fifty-five percent of these patients improved to an alignment of 10 prism diopters or less when evaluated six months or more following injection.

16 HOW SUPPLIED/STORAGE AND HANDLING**16.1 How Supplied**

BOTOX (onabotulinumtoxinA) for injection is a sterile, vacuum-dried powder supplied in a single-dose vial in the following sizes:

100 Units NDC 0023-1145-01

200 Units NDC 0023-3921-02

BOTOX cartons have features to alert users if contents may have been compromised. Each BOTOX vial label and carton also contains the U.S. License number: 1889 [see *Dosage and Administration (2.1)*].

Do not use the product and contact AbbVie for additional information at 1-800-678-1605 if the labeling is not described as above.

16.2 Storage and Handling

Unopened vials of BOTOX should be stored in a refrigerator between 2° to 8°C (36° to 46°F) for up to 36 months. Do not use after the expiration date on the vial. Reconstituted BOTOX may be stored in a refrigerator (2° to 8°C) for up to 24 hours until time of use [see *Dosage and Administration (2.2)*].

17 PATIENT COUNSELING INFORMATION

Advise the patient or caretaker to read the FDA-approved patient labeling (Medication Guide).

Swallowing, Speaking or Breathing Difficulties, or Other Unusual Symptoms

Advise patients or their caretaker(s) to inform their doctor or pharmacist if they develop any unusual symptoms (including difficulty with swallowing, speaking, or breathing), or if any existing symptom worsens [see *Boxed Warning and Warnings and Precautions (5.1, 5.6)*].

Ability to Operate Machinery or Vehicles

Advise patients or their caretaker(s) that if loss of strength, muscle weakness, blurred vision, dizziness, or drooping eyelids occur, they should avoid driving a car or engaging in other potentially hazardous activities.

Voiding Symptoms after Bladder Injections

After bladder injections for urinary incontinence, advise patients to contact their physician if they experience difficulties in voiding or burning sensation upon voiding.

Manufactured by: AbbVie Inc.

1 N Waukegan Rd. North Chicago, IL. 60064

U.S. License Number 1889

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Patented. See: <https://www.abbvie.com/patents.html>

abbvie

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MEDICATION GUIDE
BOTOX®
BOTOX® Cosmetic
(Boe-tox)
(onabotulinumtoxinA)
for injection, for intramuscular, intradetrusor,
or intradermal use

What is the most important information I should know about BOTOX and BOTOX Cosmetic?
BOTOX and BOTOX Cosmetic may cause serious side effects that can be life threatening, including:

- **Problems breathing or swallowing**
- **Spread of toxin effects**

These problems can happen hours, days, to weeks after an injection of BOTOX or BOTOX Cosmetic. Call your doctor or get medical help right away if you have any of these problems after treatment with BOTOX or BOTOX Cosmetic:

- **Problems swallowing, speaking, or breathing.** These problems can happen hours, days, to weeks after an injection of **BOTOX or BOTOX Cosmetic** usually because the muscles that you use to breathe and swallow can become weak after the injection. Death can happen as a complication if you have severe problems with swallowing or breathing after treatment with **BOTOX or BOTOX Cosmetic**.
 - People with certain breathing problems may need to use muscles in their neck to help them breathe. These people may be at greater risk for serious breathing problems with **BOTOX or BOTOX Cosmetic**.
 - Swallowing problems may last for several months. People who cannot swallow well may need a feeding tube to receive food and water. If swallowing problems are severe, food or liquids may go into your lungs. People who already have swallowing or breathing problems before receiving **BOTOX or BOTOX Cosmetic** have the highest risk of getting these problems.
- **Spread of toxin effects.** In some cases, the effect of botulinum toxin may affect areas of the body away from the injection site and cause symptoms of a serious condition called botulism. The symptoms of botulism include:
 - loss of strength and muscle weakness all over the body
 - double vision, blurred vision and drooping eyelids
 - hoarseness or change or loss of voice (dysphonia)
 - trouble saying words clearly (dysarthria)
 - loss of bladder control
 - trouble breathing
 - trouble swallowing

These symptoms can happen hours, days, to weeks after you receive an injection of BOTOX or BOTOX Cosmetic.

These problems could make it unsafe for you to drive a car or do other dangerous activities. See "What should I avoid while receiving **BOTOX or BOTOX Cosmetic**?"

There has not been a confirmed serious case of spread of toxin effect away from the injection site when **BOTOX** has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when **BOTOX Cosmetic** has been used at the recommended dose to treat frown lines, crow's feet lines, forehead lines, or vertical bands connecting the jaw and neck.

What are BOTOX and BOTOX Cosmetic?

BOTOX is a prescription medicine that is injected into muscles and used:

- to treat overactive bladder symptoms such as a strong need to urinate with leaking or wetting accidents (urge urinary incontinence), a strong need to urinate right away (urgency) and urinating often (frequency) in adults when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat leakage of urine (incontinence) in adults with overactive bladder due to neurologic disease when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to treat overactive bladder due to a neurologic disease in children 5 years of age and older when another type of medicine (anticholinergic) does not work well enough or cannot be taken.
- to prevent headaches in adults with chronic migraine who have 15 or more days each month with headache lasting 4 or more hours each day.
- to treat increased muscle stiffness in people 2 years of age and older with spasticity.
- to treat the abnormal head position and neck pain that happens with cervical dystonia (CD) in adults.
- to treat certain types of eye muscle problems (strabismus) or abnormal spasm of the eyelids (blepharospasm) in people 12 years of age and older.

BOTOX is also injected into the skin to treat the symptoms of severe underarm sweating (severe primary axillary hyperhidrosis) when medicines used on the skin (topical) do not work well enough.

BOTOX Cosmetic is a prescription medicine for adults that is injected into muscles and used for a short period of time (temporary) to improve the look of:

- moderate to severe frown lines between the eyebrows (glabellar lines)
- moderate to severe crow's feet lines
- moderate to severe forehead lines
- moderate to severe vertical bands connecting the jaw and neck (platysma bands)

You may receive treatment for frown lines, crow's feet lines, forehead lines, and vertical bands connecting the jaw and neck at the same time.

It is not known whether **BOTOX** is safe and effective in people younger than:

- 18 years of age for treatment of overactive bladder with urinary incontinence
- 5 years of age for the treatment of overactive bladder due to a neurologic disease
- 18 years of age for treatment of chronic migraine
- 16 years of age for treatment of cervical dystonia
- 18 years of age for treatment of hyperhidrosis
- 12 years of age for treatment of strabismus or blepharospasm
- 2 years of age for treatment of spasticity

BOTOX Cosmetic is not recommended for use in children younger than 18 years of age.

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe and effective to prevent headaches in people with migraine who have 14 or fewer headache days each month (episodic migraine).

It is not known whether **BOTOX** and **BOTOX Cosmetic** are safe and effective for severe sweating anywhere other than your armpits.

It is not known if **BOTOX Cosmetic** is safe and effective for use more than 1 time every 3 months.

Who should not receive BOTOX or BOTOX Cosmetic?

Do not receive **BOTOX** or **BOTOX Cosmetic** if you:

- are allergic to any of the ingredients in **BOTOX** or **BOTOX Cosmetic**. See the end of this Medication Guide for a complete list of ingredients in **BOTOX** and **BOTOX Cosmetic**.
- had an allergic reaction to any other botulinum toxin product such as Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), Xeomin® (incobotulinumtoxinA), Jeuveau® (prabotulinumtoxinA-xvfs), Daxxify® (daxibotulinumtoxinA-lanm), or Letybo® (letibotulinumtoxinA-wlbj). This may not be a complete list of all botulinum toxin products.
- have a skin infection at the planned injection site.
- are being treated for urinary incontinence and have a urinary tract infection (UTI).
- are being treated for urinary incontinence and find that you cannot empty your bladder on your own (only applies to people who are not routinely catheterizing).

What should I tell my doctor before receiving BOTOX or BOTOX Cosmetic?**Tell your doctor about all your medical conditions, including if you:**

- have a disease that affects your muscles and nerves (such as amyotrophic lateral sclerosis [ALS or Lou Gehrig's disease], myasthenia gravis or Lambert-Eaton syndrome). See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"
- have allergies to any botulinum toxin product.
- had any side effect from any botulinum toxin product in the past.
- have or have had a breathing problem, such as asthma or emphysema.
- have or have had swallowing problems.
- have or have had bleeding problems.
- have plans to have surgery.
- had surgery on your face.
- have weakness of your forehead muscles, such as trouble raising your eyebrows.
- have drooping eyelids.
- have any other change in the way your face normally looks.
- have symptoms of a urinary tract infection (UTI) and are being treated for urinary incontinence. Symptoms of a urinary tract infection may include pain or burning with urination, frequent urination, or fever.
- have problems emptying your bladder on your own and are being treated for urinary incontinence.
- are pregnant or plan to become pregnant. It is not known if **BOTOX** or **BOTOX Cosmetic** can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if **BOTOX** or **BOTOX Cosmetic** passes into breast milk.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Using **BOTOX** or **BOTOX Cosmetic** with certain other medicines may cause serious side effects. **Do not start any new medicines until you have told your doctor that you have received BOTOX or BOTOX Cosmetic in the past.**

Especially tell your doctor if you:

- have received any other botulinum toxin product in the last four months.
- have received injections of botulinum toxin, such as Myobloc® (rimabotulinumtoxinB), Dysport® (abobotulinumtoxinA), Xeomin® (incobotulinumtoxinA), Jeuveau® (prabotulinumtoxinA-xvfs), Daxxify® (daxibotulinumtoxinA-lanm), or Letybo® (letibotulinumtoxinA-wlbg) in the past. This may not be a complete list of all botulinum toxin products. Be sure your doctor knows exactly which product you received.
- have recently received an antibiotic by injection.
- take muscle relaxants.
- take an allergy or cold medicine.
- take a sleep medicine.
- take anti-platelets (aspirin-like products) or anti-coagulants (blood thinners).

Ask your doctor if you are not sure if your medicine is one that is listed above.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist each time you get a new medicine.

How will I receive BOTOX or BOTOX Cosmetic?

- **BOTOX** or **BOTOX Cosmetic** is an injection that your doctor will give you.
- **BOTOX** is injected into your affected muscles, skin, or bladder.
- **BOTOX Cosmetic** is injected into your affected muscles.
- Your doctor may change your dose of **BOTOX** or **BOTOX Cosmetic**, until you and your doctor find the best dose for you.
- **Your doctor will tell you how often you will receive your dose of BOTOX or BOTOX Cosmetic injections.**

What should I avoid while receiving BOTOX or BOTOX Cosmetic?

BOTOX and **BOTOX Cosmetic** may cause loss of strength or general muscle weakness, vision problems, or dizziness within hours to weeks of taking **BOTOX** or **BOTOX Cosmetic**. **If this happens,**

do not drive a car, operate machinery, or do other dangerous activities. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

What are the possible side effects of BOTOX and BOTOX Cosmetic?

BOTOX and BOTOX Cosmetic can cause serious side effects. See "What is the most important information I should know about **BOTOX** and **BOTOX Cosmetic**?"

Other side effects of BOTOX and BOTOX Cosmetic include:

- dry mouth.
- discomfort or pain at the injection site.
- tiredness.
- headache.
- neck pain.
- eye problems: double vision, blurred vision, decreased eyesight, drooping eyelids, swelling of your eyelids, and dry eyes.
- drooping eyebrows.
- urinary tract infection in both children and adults being treated for urinary incontinence.
- painful urination in adults being treated for urinary incontinence.
- bacteria, white blood cells, and blood in the urine of children being treated for urinary incontinence.
- inability to empty your bladder on your own and are being treated for urinary incontinence. If you have difficulty fully emptying your bladder after getting **BOTOX**, you may need to use disposable self-catheters to empty your bladder up to a few times each day until your bladder is able to start emptying again.
- allergic reactions. Symptoms of an allergic reaction to **BOTOX** or **BOTOX Cosmetic** may include: itching, rash, red itchy welts, wheezing, asthma symptoms, or dizziness or feeling faint. Tell your doctor or get medical help right away if you are wheezing or have asthma symptoms, or if you become dizzy or faint.
- upper respiratory tract infection.

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of **BOTOX** and **BOTOX Cosmetic**. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of BOTOX and BOTOX Cosmetic:

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.

This Medication Guide summarizes the most important information about **BOTOX** and **BOTOX Cosmetic**. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about **BOTOX** and **BOTOX Cosmetic** that is written for health professionals.

What are the ingredients in BOTOX and BOTOX Cosmetic?

Active ingredient: onabotulinumtoxinA

Inactive ingredients: human albumin and sodium chloride

Manufactured by: AbbVie Inc.

1 N Waukegan Rd. North Chicago, IL 60064

U.S. License Number 1889

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V8.0MG1145

This Medication Guide has been approved by the U.S. Food and Drug Administration

Revised: 10/2024

CIVIL COVER SHEET

JS-44 (Rev. 11/2020 DC)

I. (a) PLAINTIFFS AbbVie Inc. (b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF <u>88888</u> (EXCEPT IN U.S. PLAINTIFF CASES)	DEFENDANTS U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, et al. COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT _____ (IN U.S. PLAINTIFF CASES ONLY) <small>NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED</small>
(c) ATTORNEYS (FIRMNAME, ADDRESS, AND TELEPHONE NUMBER) Paul, Weiss, Rifkind, Wharton & Garrison LLP 2001 K Street, N.W. Washington, DC 20006 (202) 223-7300	ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION (PLACE AN x IN ONE BOX ONLY) <div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <input type="radio"/> 1 U.S. Government Plaintiff </div> <div style="width: 48%;"> <input type="radio"/> 3 Federal Question (U.S. Government Not a Party) </div> </div> <div style="display: flex; justify-content: space-between;"> <div style="width: 48%;"> <input checked="" type="radio"/> 2 U.S. Government Defendant </div> <div style="width: 48%;"> <input type="radio"/> 4 Diversity (Indicate Citizenship of Parties in item III) </div> </div>	III. CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN x IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT) FOR DIVERSITY CASES ONLY! <table style="width: 100%; border: none;"> <thead> <tr> <th></th> <th style="text-align: center;">PTF</th> <th style="text-align: center;">DFT</th> <th></th> <th style="text-align: center;">PTF</th> <th style="text-align: center;">DFT</th> </tr> </thead> <tbody> <tr> <td>Citizen of this State</td> <td style="text-align: center;"><input type="radio"/> 1</td> <td style="text-align: center;"><input type="radio"/> 1</td> <td>Incorporated or Principal Place of Business in This State</td> <td style="text-align: center;"><input type="radio"/> 4</td> <td style="text-align: center;"><input type="radio"/> 4</td> </tr> <tr> <td>Citizen of Another State</td> <td style="text-align: center;"><input type="radio"/> 2</td> <td style="text-align: center;"><input type="radio"/> 2</td> <td>Incorporated and Principal Place of Business in Another State</td> <td style="text-align: center;"><input type="radio"/> 5</td> <td style="text-align: center;"><input type="radio"/> 5</td> </tr> <tr> <td>Citizen or Subject of a Foreign Country</td> <td style="text-align: center;"><input type="radio"/> 3</td> <td style="text-align: center;"><input type="radio"/> 3</td> <td>Foreign Nation</td> <td style="text-align: center;"><input type="radio"/> 6</td> <td style="text-align: center;"><input type="radio"/> 6</td> </tr> </tbody> </table>		PTF	DFT		PTF	DFT	Citizen of this State	<input type="radio"/> 1	<input type="radio"/> 1	Incorporated or Principal Place of Business in This State	<input type="radio"/> 4	<input type="radio"/> 4	Citizen of Another State	<input type="radio"/> 2	<input type="radio"/> 2	Incorporated and Principal Place of Business in Another State	<input type="radio"/> 5	<input type="radio"/> 5	Citizen or Subject of a Foreign Country	<input type="radio"/> 3	<input type="radio"/> 3	Foreign Nation	<input type="radio"/> 6	<input type="radio"/> 6
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Citizen or Subject of a Foreign Country	<input type="radio"/> 3	<input type="radio"/> 3	Foreign Nation	<input type="radio"/> 6	<input type="radio"/> 6																				

IV. CASE ASSIGNMENT AND NATURE OF SUIT

(Place an X in one category, A-N, that best represents your Cause of Action and one in a corresponding Nature of Suit)

<input type="radio"/> A. Antitrust <input type="checkbox"/> 410 Antitrust	<input type="radio"/> B. Personal Injury/Malpractice <input type="checkbox"/> 310 Airplane <input type="checkbox"/> 315 Airplane Product Liability <input type="checkbox"/> 320 Assault, Libel & Slander <input type="checkbox"/> 330 Federal Employers Liability <input type="checkbox"/> 340 Marine <input type="checkbox"/> 345 Marine Product Liability <input type="checkbox"/> 350 Motor Vehicle <input type="checkbox"/> 355 Motor Vehicle Product Liability <input type="checkbox"/> 360 Other Personal Injury <input type="checkbox"/> 362 Medical Malpractice <input type="checkbox"/> 365 Product Liability <input type="checkbox"/> 367 Health Care/Pharmaceutical Personal Injury Product Liability <input type="checkbox"/> 368 Asbestos Product Liability	<input type="radio"/> C. Administrative Agency Review <input type="checkbox"/> 151 Medicare Act <u>Social Security</u> <input type="checkbox"/> 861 HIA (1395ff) <input type="checkbox"/> 862 Black Lung (923) <input type="checkbox"/> 863 DIWC/DIWW (405(g)) <input type="checkbox"/> 864 SSID Title XVI <input type="checkbox"/> 865 RSI (405(g)) <u>Other Statutes</u> <input type="checkbox"/> 891 Agricultural Acts <input type="checkbox"/> 893 Environmental Matters <input type="checkbox"/> 890 Other Statutory Actions (If Administrative Agency is Involved)	<input type="radio"/> D. Temporary Restraining Order/Preliminary Injunction Any nature of suit from any category may be selected for this category of case assignment. *(If Antitrust, then A governs)*
<input checked="" type="radio"/> E. General Civil (Other) OR <input type="radio"/> F. Pro Se General Civil			
<u>Real Property</u> <input type="checkbox"/> 210 Land Condemnation <input type="checkbox"/> 220 Foreclosure <input type="checkbox"/> 230 Rent, Lease & Ejectment <input type="checkbox"/> 240 Torts to Land <input type="checkbox"/> 245 Tort Product Liability <input type="checkbox"/> 290 All Other Real Property <u>Personal Property</u> <input type="checkbox"/> 370 Other Fraud <input type="checkbox"/> 371 Truth in Lending <input type="checkbox"/> 380 Other Personal Property Damage <input type="checkbox"/> 385 Property Damage Product Liability	<u>Bankruptcy</u> <input type="checkbox"/> 422 Appeal 28 USC 158 <input type="checkbox"/> 423 Withdrawal 28 USC 157 <u>Prisoner Petitions</u> <input type="checkbox"/> 535 Death Penalty <input type="checkbox"/> 540 Mandamus & Other <input type="checkbox"/> 550 Civil Rights <input type="checkbox"/> 555 Prison Conditions <input type="checkbox"/> 560 Civil Detainee – Conditions of Confinement <u>Property Rights</u> <input type="checkbox"/> 820 Copyrights <input type="checkbox"/> 830 Patent <input type="checkbox"/> 835 Patent – Abbreviated New Drug Application <input type="checkbox"/> 840 Trademark <input type="checkbox"/> 880 Defend Trade Secrets Act of 2016 (DTSA)	<u>Federal Tax Suits</u> <input type="checkbox"/> 870 Taxes (US plaintiff or defendant) <input type="checkbox"/> 871 IRS-Third Party 26 USC 7609 <u>Forfeiture/Penalty</u> <input type="checkbox"/> 625 Drug Related Seizure of Property 21 USC 881 <input type="checkbox"/> 690 Other <u>Other Statutes</u> <input type="checkbox"/> 375 False Claims Act <input type="checkbox"/> 376 Qui Tam (31 USC 3729(a)) <input type="checkbox"/> 400 State Reapportionment <input type="checkbox"/> 430 Banks & Banking <input type="checkbox"/> 450 Commerce/ICC Rates/etc <input type="checkbox"/> 460 Deportation <input type="checkbox"/> 462 Naturalization Application	<input type="checkbox"/> 465 Other Immigration Actions <input type="checkbox"/> 470 Racketeer Influenced & Corrupt Organization <input type="checkbox"/> 480 Consumer Credit <input type="checkbox"/> 485 Telephone Consumer Protection Act (TCPA) <input type="checkbox"/> 490 Cable/Satellite TV <input type="checkbox"/> 850 Securities/Commodities/Exchange <input type="checkbox"/> 896 Arbitration <input checked="" type="checkbox"/> 899 Administrative Procedure Act/Review or Appeal of Agency Decision <input type="checkbox"/> 950 Constitutionality of State Statutes <input type="checkbox"/> 890 Other Statutory Actions (if not administrative agency review or Privacy Act)

<input type="radio"/> G. Habeas Corpus/ 2255 <input type="checkbox"/> 530 Habeas Corpus – General <input type="checkbox"/> 510 Motion/Vacate Sentence <input type="checkbox"/> 463 Habeas Corpus – Alien Detainee	<input type="radio"/> H. Employment Discrimination <input type="checkbox"/> 442 Civil Rights – Employment (criteria: race, gender/sex, national origin, discrimination, disability, age, religion, retaliation) *(If pro se, select this deck)*	<input type="radio"/> I. FOIA/Privacy Act <input type="checkbox"/> 895 Freedom of Information Act <input type="checkbox"/> 890 Other Statutory Actions (if Privacy Act) *(If pro se, select this deck)*	<input type="radio"/> J. Student Loan <input type="checkbox"/> 152 Recovery of Defaulted Student Loan (excluding veterans)
<input type="radio"/> K. Labor/ERISA (non-employment) <input type="checkbox"/> 710 Fair Labor Standards Act <input type="checkbox"/> 720 Labor/Mgmt. Relations <input type="checkbox"/> 740 Labor Railway Act <input type="checkbox"/> 751 Family and Medical Leave Act <input type="checkbox"/> 790 Other Labor Litigation <input type="checkbox"/> 791 Empl. Ret. Inc. Security Act	<input type="radio"/> L. Other Civil Rights (non-employment) <input type="checkbox"/> 441 Voting (if not Voting Rights Act) <input type="checkbox"/> 443 Housing/Accommodations <input type="checkbox"/> 440 Other Civil Rights <input type="checkbox"/> 445 Americans w/Disabilities – Employment <input type="checkbox"/> 446 Americans w/Disabilities – Other <input type="checkbox"/> 448 Education	<input type="radio"/> M. Contract <input type="checkbox"/> 110 Insurance <input type="checkbox"/> 120 Marine <input type="checkbox"/> 130 Miller Act <input type="checkbox"/> 140 Negotiable Instrument <input type="checkbox"/> 150 Recovery of Overpayment & Enforcement of Judgment <input type="checkbox"/> 153 Recovery of Overpayment of Veteran's Benefits <input type="checkbox"/> 160 Stockholder's Suits <input type="checkbox"/> 190 Other Contracts <input type="checkbox"/> 195 Contract Product Liability <input type="checkbox"/> 196 Franchise	<input type="radio"/> N. Three-Judge Court <input type="checkbox"/> 441 Civil Rights – Voting (if Voting Rights Act)

V. ORIGIN
☒ 1 Original Proceeding
 ☐ 2 Removed from State Court
 ☐ 3 Remanded from Appellate Court
 ☐ 4 Reinstated or Reopened
 ☐ 5 Transferred from another district (specify)
 ☐ 6 Multi-district Litigation
 ☐ 7 Appeal to District Judge from Mag. Judge
 ☐ 8 Multi-district Litigation – Direct File

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE.)
 Plaintiff challenges, under 5 U.S.C. 702, the defendants' selection of BOTOX for Inflation Reduction Act price controls.

VII. REQUESTED IN COMPLAINT

☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23

DEMAND \$

JURY DEMAND:

Check YES only if demanded in complaint
 YES ☐ NO ☒

VIII. RELATED CASE(S) IF ANY

(See instruction)

YES ☐ NO ☒

If yes, please complete related case form

DATE: 2/11/2026

SIGNATURE OF ATTORNEY OF RECORD /s/ Kannon K. Shanmugam

INSTRUCTIONS FOR COMPLETING CIVIL COVER SHEET JS-44
 Authority for Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and services of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently, a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. Listed below are tips for completing the civil coversheet. These tips coincide with the Roman Numerals on the cover sheet.

- I.** COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF/DEFENDANT (b) County of residence: Use 11001 to indicate plaintiff if resident of Washington, DC, 88888 if plaintiff is resident of United States but not Washington, DC, and 99999 if plaintiff is outside the United States.
- III.** CITIZENSHIP OF PRINCIPAL PARTIES: This section is completed only if diversity of citizenship was selected as the Basis of Jurisdiction under Section II.
- IV.** CASE ASSIGNMENT AND NATURE OF SUIT: The assignment of a judge to your case will depend on the category you select that best represents the primary cause of action found in your complaint. You may select only one category. You must also select one corresponding nature of suit found under the category of the case.
- VI.** CAUSE OF ACTION: Cite the U.S. Civil Statute under which you are filing and write a brief statement of the primary cause.
- VIII.** RELATED CASE(S), IF ANY: If you indicated that there is a related case, you must complete a related case form, which may be obtained from the Clerk's Office.

Because of the need for accurate and complete information, you should ensure the accuracy of the information provided prior to signing the form.

AO 440 (Rev. 06/12; DC 3/15) Summons in a Civil Action

UNITED STATES DISTRICT COURT

for the

District of Columbia

ABBVIE INC.

Plaintiff(s)

v.

U.S. DEPARTMENT OF HEALTH AND HUMAN
SERVICES, et al.

Defendant(s)

Civil Action No.

SUMMONS IN A CIVIL ACTION

To: *(Defendant's name and address)* U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
200 Independence Avenue, S.W.
Washington, DC 20201

A lawsuit has been filed against you.

Within 21 days after service of this summons on you (not counting the day you received it) — or 60 days if you are the United States or a United States agency, or an officer or employee of the United States described in Fed. R. Civ. P. 12 (a)(2) or (3) — you must serve on the plaintiff an answer to the attached complaint or a motion under Rule 12 of the Federal Rules of Civil Procedure. The answer or motion must be served on the plaintiff or plaintiff's attorney, whose name and address are:

Kannon K. Shanmugam
PAUL, WEISS, RIFKIND, WHARTON & GARRISON LLP
2001 K Street, N.W.
Washington, DC 20006
(202) 223-7300

If you fail to respond, judgment by default will be entered against you for the relief demanded in the complaint. You also must file your answer or motion with the court.

ANGELA D. CAESAR, CLERK OF COURT

Date: _____

Signature of Clerk or Deputy Clerk

Civil Action No. _____

PROOF OF SERVICE*(This section should not be filed with the court unless required by Fed. R. Civ. P. 4 (l))*

This summons for *(name of individual and title, if any)* _____
 was received by me on *(date)* _____ .

☐ I personally served the summons on the individual at *(place)* _____
 _____ on *(date)* _____ ; or

☐ I left the summons at the individual's residence or usual place of abode with *(name)* _____
 _____ , a person of suitable age and discretion who resides there,
 on *(date)* _____ , and mailed a copy to the individual's last known address; or

☐ I served the summons on *(name of individual)* _____ , who is
 designated by law to accept service of process on behalf of *(name of organization)* _____
 _____ on *(date)* _____ ; or

☐ I returned the summons unexecuted because _____ ; or

☐ Other *(specify)*: _____

My fees are \$ _____ for travel and \$ _____ for services, for a total of \$ _____ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____

Server's signature

Printed name and title

Server's address

Additional information regarding attempted service, etc:

District of Columbia

Civil Action No.

Signature of Clerk or Deputy Clerk

Civil Action No. _____

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