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Background Information on Public Citizen's Petition to the FDA Regarding Botox and Related Drugs and Pertinent Postmarketing Evidence

On December 12, 2023, Public Citizen submitted a citizen petition to the U.S. Food and Drug Administration (FDA) regarding the labeling of all seven approved botulinum toxin biological drugs (hereafter, Botox and related drugs): abobotulinumtoxinA (Dysport), daxibotulinumtoxinA-lanm (Daxxify), incobotulinumtoxinA (Xeomin), onabotulinumtoxinA (Botox, Botox Cosmetic), prabotulinumtoxinA-xvfs (Jeuveau) and rimabotulinumtoxinB (Myobloc).

Specifically, the petition urges the FDA to promptly take two actions:

1) Strengthen the black box warning (the most prominent warning) in the labeling of all approved Botox and related drugs, and

2) Remove misleading promotional statements from the labeling of Botox and Botox Cosmetic.

The petition is based on evidence from the medical literature published after these drugs were first marketed as well as a primary Public Citizen analysis of data from the FDA Adverse Event Reporting System (FAERS), a database that contains voluntary reports of drug-related adverse events.

Botox and related drugs are injectable drugs purified from botulinum toxin, a poison derived from the bacterium *Clostridium botulinum*, which causes botulism, a muscle-paralyzing disease that can be fatal. Injections of these drugs temporarily block the nerve signals that cause muscles to contract. Therefore, they have been approved to treat several conditions including cervical dystonia (involuntary contraction of the neck muscles), severe underarm sweating, blepharospasm (abnormal spam of the eyelids), spasticity of limb muscles, and strabismus (certain types of eye muscle problems), as well as for preventing chronic migraine. Botox and related drugs also are approved to treat certain cosmetic conditions: smoothing crow's feet lines, forehead lines, and frown lines.

Information about the current black box warning in the labeling of Botox and related drugs and its main shortcomings:

- In 2008, Public Citizen petitioned the FDA to require the addition of the black box warning on the labeling of Botox and related drugs regarding the risk of distant spread of the toxin (spread beyond the site of the local injection to other parts of the body), a request that the agency granted in 2009.

- However, the current black box warning fails to explicitly mention the risk of "systemic iatrogenic botulism" — a complication of treatment with Botox and related drugs due to their potential for diffusion and systemic spread beyond injection sites, causing progressive, typically descending muscle paralysis or weakness and related symptoms.
    - The current black box warning notes that these medications "may spread from the area of injection to produce symptoms (such as asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties) that are consistent with botulinum toxin effects. All these symptoms are those of iatrogenic botulism.
    - The term "botulism" is only mentioned in the labeling of Botox and related drugs once, toward the end.
- Although the current black box warning acknowledges that distant spread has occurred in "approved indications… at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses," it does not explicitly state that there is evidence that iatrogenic botulism and botulism-related symptoms have occurred after <u>both initial and subsequent injections of recommended botulinum toxin doses for various approved uses</u>.
- Finally, the current black box warning does not include any information about botulinum antitoxin, the only specific therapy for all types of botulism. Early administration of botulinum antitoxin is critical to prevent progression of botulism, including temporary paralysis and respiratory failure.
- Also, the general warnings section regarding botulinum toxin overdose in the labeling of Botox and related drugs downplays the need for administering botulinum antitoxin in the contexts of excessive dosing, accidental injection, and oral ingestion of these drugs.

What Public Citizen is asking the FDA to change in the black box warning of Botox and related drugs:

- We are asking the agency to require the manufacturers of all Botox and related drugs to make it clear that, even when used at recommended doses, either in initial or subsequent (repeated) treatment, these drugs are associated with systemic iatrogenic botulism and related symptoms.
- We also are asking the FDA to make it clear that cases of systemic iatrogenic botulism associated with recommended doses of Botox and related drugs may require prompt administration of botulinum antitoxin to avoid disease progression and serious outcomes, including temporary muscle paralysis, hospitalization, and death.

The postmarketing evidence that Public Citizen used to support our request for changes to the black box warning:

- Our petition discusses several published drug safety case reports and case series that show that systemic iatrogenic botulism has occurred with recommended doses of Botox and related drugs for various approved uses.
- Our primary analysis of the FAERS database identified 5,414 reports with serious outcomes — such as death, life-threatening events, hospitalization, or disability — in which Botox or a related drug was the only primary suspect. The reports were from January 1989 through March 2021.

- Of those 5,414 serious reports, 121 (2%) specified botulism (i.e., iatrogenic botulism, as they occurred following injection of Botox or related drugs) as an adverse reaction: 89 involved therapeutic uses of Botox or a related drug and 32 involved cosmetic uses.
    - Several of these 121 botulism reports involved botulinum toxin doses that are within the recommended dose range for the specified use. For example, seven of 27 botulism reports involving Botox Cosmetic indicated that the injected doses ranged from 10 to 30 units (the maximum recommended dose is 20 to 40 units). In addition, five of the 66 botulism reports involving therapeutic uses of Botox indicated that the injected doses were 50 or fewer units (the maximum recommended dose ranges from 100 to 400 units).
- We also found that 2,817 (52%) of the total 5,414 serious reports included signs or symptoms that are suggestive of iatrogenic botulism, consistent with the effect of Botox and related drugs. We grouped iatrogenic botulism-suggestive signs or symptoms into six categories: 1) those involving the urinary bladder, 2) those involving muscle weakness or paralysis (in the extremities), 3) those involving the eyes, 4) those involving the oropharynx (area in the back of the mouth and upper throat), 5) those involving breathing, and 6) those involving certain abnormal sensations (paranesthesia, peripheral sensory neuropathy, and hypoesthesia).
    - Many of these 2,817 reports involved small doses of Botox or related drugs.
- Our analysis may greatly underestimate the true incidence of serious adverse events associated with Botox and related drugs — including those of iatrogenic botulism and its suggestive signs or symptoms — due to the voluntary reporting of adverse events to the FAERS database. A systematic review estimated that only 6% of the adverse events of drugs are reported to spontaneous reporting systems, such as the FAERS database.

Why the FDA should require removal of misleading statements regarding Botox and Botox Cosmetic:

- We are asking the FDA to require the removal of three misleading promotional statements from the labeling of Botox and Botox Cosmetic. The claims are "[n]o definitive serious adverse event reports of distant spread of toxin effect" associated with the use of recommended doses of these drugs to treat four therapeutic indications (blepharospasm, chronic migraine, severe underarm sweating, and strabismus) and certain approved cosmetic uses.
- The above claims are refuted by the following facts:
    - No such statements are part of similar drug labeling in other countries, such as Canada and the United Kingdom.
    - Of 639 serious reports in the FAERS database that we identified in which Botox was the primary suspect when used to treat one of the four therapeutic indications listed in the misleading claims, 269 (42%) included adverse reactions that were suggestive of iatrogenic botulism. Many of those 269 reports involved recommended initial or repeated doses of Botox.
    - Of 934 reports to the FAERS database that we identified in which Botox Cosmetic was the primary suspect, at least 140 initial or single-dose reports and at least 24 repeated dose reports involved doses of 30 units or less; some reports were of doses as low as six units.