FDA Request for Class Labeling for Botulinum Toxin Treatments

Botulinum toxin products have been approved by the US Food and Drug Administration (FDA) for one or more of the following uses:

- Temporary improvement in the appearance of glabellar lines (frown lines between the eyebrows)
- Treatment of strabismus (crossed eyes)
- Blepharospasm (abnormal tics and twitches of the eyelids)
- Cervical dystonia (involuntary sustained or repetitive contraction of the neck muscles)
- Primary axillary hyperhidrosis (severe underarm sweating)
- Spasticity in the flexor muscles of the elbow, wrist, and fingers in adults
- Treatment of overactive bladder
- Treatment of chronic migraine

For these uses, botulinum toxin is injected into skin or muscle tissue.

As a result of an ongoing safety review, the FDA has notified the manufacturers of licensed botulinum toxin products to:

- Add *a boxed warning* regarding the risk of adverse events when the effects of the toxin spread beyond the site where it was injected
- Develop and implement a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the product outweigh the risks. The REMS would include:
    - Communication plan
        - To provide more information regarding the risk of distant spread of botulinum toxin effects after local injection
        - To explain that botulinum toxin products cannot be interchanged
    - Medication guide to explain the risks to patients and their families and caregivers
- Submit safety data after multiple administrations of the product in a specified number of children and adults with spasticity to assess the potential risk of distant spread of toxin effects

Postmarketing Review

The following information summarizes the FDA's review of postmarketing safety data obtained from the manufacturers of botulinum toxin products and all existing data within the FDA regarding these adverse events:

- In *pediatric* postmarketing adverse event case reports, botulinum toxin products were mostly used to treat muscle spasticity in cerebral palsy, a use that has not been approved by the FDA. The reported cases of spread of botulinum toxin effect beyond the site of injection were described as botulism or involved symptoms including difficulty breathing, difficulty swallowing, muscle weakness, drooping eyelids, constipation, aspiration pneumonia, speech disorder, facial drooping, double vision, or respiratory depression. Serious case reports described hospitalizations involving ventilatory support and reports of death.

- The majority of the *adult* postmarketing case reports of distant spread of toxin effects occurred following the use of botulinum toxin for the treatment of spasticity (an approved use for UE spasticity) or cervical dystonia. Some cases resulted in hospitalization, including several cases that required placement of a gastric tube or mechanical ventilation. Although there were several deaths in adults, it is not possible to attribute them to the botulinum toxin because the patients also suffered from complications of their preexisting conditions. In addition, some reports show that symptoms could be consistent with distant spread of toxin effect following dermatologic use. However, no definitive serious adverse event reports of distant spread of toxin effect associated with dermatologic use of botulinum toxin type A at the labeled dose of 20 units (for glabellar lines) or 100 units (for primary axillary hyperhidrosis) have been identified.

Recommendations

The FDA's evaluation of the data continues to support the recommendations made in the Early Communication that healthcare professionals who use botulinum toxin products should:

- Understand that dosage strengths (potency) expressed in "units" or "U" differ among the botulinum toxin products: Clinical doses expressed in units are not interchangeable from one botulinum toxin product to another
- Be alert to and educate patients and caregivers about potential adverse events due to distant spread of botulinum toxin effects following local injections:
    - Unexpected loss of strength or muscle weakness
    - Hoarseness or trouble talking (dysphonia)
    - Trouble saying words clearly (dysarthria)
    - Loss of bladder control
    - Trouble breathing
    - Trouble swallowing
    - Double vision
    - Blurred vision
    - Drooping eyelids
- Understand that these adverse events have been reported as early as several hours and as late as several weeks after treatment
- Advise patients to seek immediate medical attention if any of these symptoms develop