DaxibotulinumtoxinA (DAXXIFY) in Cervical Dystonia
National Drug Mini-Monograph
April 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL INFORMATION[1]

Description / MOA	Botulinum toxin / Neuromuscular blocking agent
Indication Under Review	Cervical Dystonia (CD)
Dosage Regimen	125 to 250 Units intramuscularly (IM) among affected muscles no more frequently than every 3 months.
Dosage Forms Under Review	50 Units or 100 Units sterile lyophilized powder in a single-dose vial.

EFFICACY CONSIDERATIONS

Trial Design: **Phase II – dose escalation study (n=34)[2]**

Design: **Primary endpoint:** change in TWSTRS total score from baseline to week 4. Patients were monitored for lasting efficacy through 24 weeks. Patients could re-enroll in a higher dose cohort (3 did this, hence 37 sets of data from 34 participants)

Population: **Key inclusion criteria:** 30-75 years old, TWSTRS total score of 20 or higher with severity subscale of at least 15, any medications taken for dystonia needed to be stable for at least 3 months prior to entry.

Key exclusion criteria: predominant retrocollis or anterocollis, CD attributed to underlying etiology (e.g. drug induced), use of any botulinum toxin within 6 months prior to screening.

76% of participants were female, 85% of participants were white. 46% had been treated with a botulinum toxin before. The average baseline TWSTRS total score was 44.1.

Intervention: Three dose cohorts: low-dose Cohort 1 (100-200 Units), moderate-dose Cohort 2 (200-300 Units), or high-dose Cohort 3 (300-450 Units). For results, dosing groups were split in 2: 100-240 Units and 300-450 Units.

Select Results:

Mean change (±SD) in TWSTRS total score				% Patients achieving ≥20% reduction in TWSTR total)
Week	DAXI 100U-240U (n=21)	DAXI 300U-450U (n=16)	Overall (DAXI 100U-450U, n=37)	Overall (DAXI 100U-450U, n=37)
4 (primary endpoint)	-16.5 (11.26)	-17.2 (6.41)	-16.8 (9.51)	83%
6	-21.7 (10.27)	-21 (11.84)	-21.3 (10.93)	94%
12	-20.4 (8.46)	-15.4 (8.36)	-18.1 (8.65)	79%
16	-16.5 (9.82)	-17 (8.39)	-16.7 (9.13)	77%
20	-16.6 (11.84)	-15.9 (10.64)	-16.3 (11.16)	74%
24	-10.1 (10.45)	-16.3 (9.17)	-12.8 (10.19)	68%

Trial Design: **Phase III - ASPEN-1 (n=301)[3]**

Design: 36-week randomized, double-blind, placebo-controlled study

Primary endpoint: change in baseline TWSTRS total score averaged across weeks 4 and 6

Population: **Key inclusion criteria:** 18-80 years old, TWSTRS total score of 20 or higher with subscales for severity, disability, and pain of ≥15, ≥3, and ≥1 respectively, any other medications taken for dystonia needed to be stable for at least 4 weeks prior to entry.

Key exclusion criteria: predominant retrocollis or anterocollis, severe dysphagia (grade 3 or 4 on Dysphagia Severity Scale), CD attributed to underlying etiology (e.g. drug induced), use of any botulinum toxin within 14 weeks prior to screening, current treatment for dystonia in other body areas, had historically required less than 100 units of onabotulinumtoxinA, suboptimal response to last botulinum toxin treatment, historical primary or secondary nonresponse to botulinum toxin injections for CD, or known neutralizing antibodies to botulinum toxin A.

64.8% of participants were female, 95.3% of participants were white. 86.4% had been treated with a botulinum toxin before. The average baseline TWSTRS total score was slightly higher in placebo group (45.3) than in DAXI groups (43.1 for 125U group and 42.6 for 250U group).

Intervention: Single dose of: DAXI 125U or DAXI 250U

Comparator: Placebo

Select Results: **Primary endpoint** - Least squares mean change from baseline to average across weeks 4 and 6 (SE): **DAXI 125U:** -12.7 (1.3); **DAXI 250U:** -10.9 (1.25); **PBO** -4.3 (1.82). Least squares mean (SE) difference vs. PBO: −8.5 (1.93) for DAXI 125U ($p < 0.0001$) and −6.6 (1.92) for DAXI 250U ($p = 0.0006$). Difference between DAXI doses was not significant.

Median duration of effect (time from treatment to loss of ≥80% of peak effect) – 24 weeks with DAXI 125U and 20.3 weeks with DAXI 250U. However, in post hoc analysis of patients who requested retreatment, 36% of

		patients on DAXI 125U and 20.8% of patients on DAXI 250U requested treatment before loss of 80% of peak effect.
	Trial Design	**Phase III OLE – APEN-OLS**
	Brief Description	ASPEN-OLS included 271 participants form ASPEN-1 and 86 newly enrolled subjects, followed for up to 36 weeks. Preliminary results published on ClinicalTrials.gov (NCT03617367). Quality review has not concluded.

Key: CD= cervical dystonia; DAXI = daxibotulinumtoxinA; PBO = placebo; SD = standard deviation; SE = standard error; TWSTRS = Toronto Western Spasmodic Torticollis Rating Scale; U = units

SAFETY CONSIDERATIONS[1]	
Boxed Warnings	**Distant spread of toxin:** It is possible that the effect of daxibotulinumtoxinA may spread beyond the area of injection (similar to risk with other botulinum toxins). Symptoms may appear hours to weeks after injection and could range in symptomology depending on injection sites. Difficulty swallowing or breathing may be life threatening. There have been reports of death with botulinum toxin spread. Certain underlying conditions may increase this risk (see below, "Neuromuscular compromise").
Contraindications	- **Known hypersensitivity** to botulinum toxins or any other component in daxibotulinumtoxinA formulation - **Infection** at the injection site
Other Warnings	- **Interchangeability:** There is currently no established unit to unit conversion from daxibotulinumtoxinA to other botulinum toxins - **Cardiovascular system adverse events:** Events such as arrhythmia and myocardial infarction have been reported with botulinum toxins. Use caution in patients with pre-existing cardiovascular disease - **Neuromuscular compromise:** Patients with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (e.g. myasthenia gravis) may be at an increased risk for increased neuromuscular compromise including muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise.
Top 5 AEs	Headache, dysphagia, injection site erythema or bruising, injection site pain, and muscular weakness
Drug Interactions	No pharmacokinetic drug interactions have been identified. Additive neuromuscular blocking effect may be seen with concurrent use of aminoglycosides, anticholinergic drugs, muscle relaxants, or other agents interfering with neuromuscular transmission.

THERAPEUTIC ALTERNATIVES			
	Drug	**Available Products**	**Labelled Dosage for CD**
	abobotulinumtoxinA (DYSPORT)	300U vial, 500U vial	500 U
	daxibotulinumtoxinA (DAXXIFY)	100U vial	125 - 250 U
	incobotulinumtoxinA (XEOMIN)	50U vial, 100U vial 200U vial	120-400 U
	onabotulinumtoxinA (BOTOX)	100U vial, 200U vial	200-360 U
	rimabotulinumtoxinB (MYOBLOC)	2,500U vial, 5,000U vial, 10,000U vial	2,000 – 5,000 U

Conclusions/Projected Place in Therapy

- The American Academy of Neurology (AAN) 2016 practice guideline update on botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache indicates botulinum toxins as a first line option for the treatment of CD.[4]
- All botulinum toxins currently approved for non-cosmetic uses are FDA approved for CD. There is currently insufficient evidence to support that any one of these toxins is more efficacious than another for CD.
- All botulinum toxins currently approved for CD, including daxibotulinumtoxinA, have a labelled dosing interval of no more frequent than every 12 - 16 weeks. Evidence from daxibotulinumtoxinA's phase II and III trials for CD indicate that treatment effect may last longer than 12 weeks and injection intervals may be able to be prolonged. However, it should be noted that 20-36% of patients on daxibotulinumtoxinA in ASPEN-1 requested retreatment while they were still considered to be prior to the defined "loss of effect" point. Thus, the practical likelihood of extended intervals may differ from loss of efficacy analysis in clinical trials. Other botulinum toxins have also shown prolonged efficacy and may also be able to be dosed less frequent than the minimum three-month interval.[5]

References

1. DaxibotulinumtoxinA (DAXXIFY®) [prescribing information online] Revance Therapeutics. Newark, CA; August 2023
2. Jankovic J, Truong D, Patel AT, et al. Injectable daxibotulinumtoxinA in cervical dystonia: a phase 2 dose-escalation multicenter study. Mov Disord. 2018; 5(3): 273-282
3. Comella CL, Jankovic J, Hauser RA, et al. Efficacy and safety of daxibotulinumtoxinA for injection in cervical dystonia. Neurology. 2024; 102:e208091
4. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache. Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016; 86(19): 1818-1826
5. Truong D, Duane DD, Jankovic J, et al. Efficacy and safety of botulinum type A toxin (Dysport) in cervical dystonia: results of the first US randomized, double-blind, placebo-controlled study. Mov Disord. 2005 Jul; 20(7):783-791

Prepared: April 2024 Contact person: N. Antonovich, PharmD, BCPS, National PBM Clinical Pharmacy Program Manager, Formulary Management, VA Pharmacy Benefits Management Services (12PBM)