Summary Review

Date	June 14, 2019
From	Gerald D. Podskalny, DO, MPHS
Subject	Summary Review
NDA/BLA # Supplement#	BLA 103000 (S-5309)
Applicant	Allergan
Date of Submission	12/20/2018
PDUFA Goal Date	6/20/2019
Proprietary Name / Established (USAN) names	Botox /onabotulinumtoxinA
Dosage forms / Strength	Injection, for intramuscular, intradetrusor, or intradermal use / 50 U, 100 U, and 200 U vials
Proposed Indication(s)	Treatment of pediatric spasticity
Recommended:	**Approval**

1. Background

FDA first approved Botox (onabotulinumtoxinA) in 1991 for the treatment of strabismus and blepharospasm. Botox is also approved for the treatment of upper and lower limb spasticity in adult patients, chronic migraine, urinary incontinence due to detrusor overactivity, hyperhidrosis, and cervical dystonia.

Allergan submitted a BLA supplement for the (b) (4) treatment of upper limb spasticity (S-5309), discussed in this memo. (b) (4) The upper limb spasticity indication received priority review status because there are no approved treatments for pediatric upper limb spasticity. (b) (4)

(b) (4) S-5309 (b) (4) also submitted to address outstanding postmarketing requirements (PMR) and (b) (4) postmarketing commitments (PMC) for studies in children ages 2 to less than 17 years for the treatment of upper (b) (4) limb spasticity. The applicant also submitted results from nonclinical juvenile toxicology studies to address the related PMR.

The review team for supplement S-5309 is presented in Table 1.

Table 1: Review team

Primary Reviewer	Review Discipline	Recommended Action
Xiangmin Zhang, Ph.D.	Office of Biostatistics	Approval
Susanne R. Goldstein, M.D.	Medical Reviewer	Approval
Briana Rider, PharmD	Labeling Safety Review	Approval
Barbara Wilcox, PhD.	Pharmacology/Toxicology	Approval

2. CMC/Device

The approved Botox (onabotulinumtoxinA) product was used for the clinical trial submitted in this application. The submission did not include new CMC information.

3. Nonclinical Pharmacology/Toxicology

Dr. Wilcox reviewed the results from a dose-ranging study and a pivotal juvenile animal toxicology study conducted in rats. Concurrence is provided by Lois Freed, PhD., nonclinical supervisor. Dr. Wilcox was unable to draw conclusions from the results of the dose-ranging study because the study did not include a control group.

In the pivotal study, Botox was injected into the left gastrocnemius muscle at increasing doses up to 24 U/kg. Dr. Wilcox concluded there were no Botox-related effects on a complete set of developmental endpoints. The observed musculoskeletal adverse effects were consistent with the known pharmacological activity of botulinum toxins. In addition to the expected changes in muscular and skeletal development, degeneration of the seminiferous tubules and abnormal spermatids were observed in the 1 of 10 mid-dose and 3 of 10 high-dose male animals. The nonclinical review team concluded the findings were clearly dose-related, and a relationship to Botox that may be relevant to humans cannot be ruled out.

The nonclinical team concluded that: 1) the data are adequate to support approval for use in the pediatric population, and 2) PMR # (b) (4) has been fulfilled. A description of the findings and recommendations based on the review of this study will be added to section 8.4 of the label.

4. Clinical/Statistical- Efficacy

Supplement S-5309 for the treatment of upper limb (UL) spasticity in children 2 to less than 17 years of age is supported by information from a single controlled safety and efficacy study (191622-101) with long-term open-label safety information from Study 191622-105.

Dr. Xiangmin Zhang, Ph.D., is the primary statistical reviewer for this application. Supervisory clearance was provided by Kun Jin, PhD., Team Leader, and Hsien Ming Hung, Ph.D., Director, Division of Biometrics I.

The placebo-controlled study 191622-101 (upper limb) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, of 16-week duration, and evaluated 2 doses of Botox versus placebo. The study consisted of a screening period lasting up to four weeks, followed by randomization and a 12-week double-blind treatment phase. Patients received a single treatment with study medication, with post-injection follow-up visits at Weeks 2, 4, 6, 8, and 12 after injection. Patients also received a standardized rehabilitation therapy regimen.

The treatment blind was maintained by a blinded “Independent Drug Reconstitutor” who diluted the Botox to the appropriate concentration for each dose group or placebo. The volume and the number of injections in each required muscle group was identical in the respective studies.

Patients who completed the respective controlled study without major protocol deviations were given the option of enrolling in open-label extension Study 191622-105.

Study 191622-101 (referred to as Study 101 in the remainder of this review) enrolled 235 patients at 40 centers, including 16 sites in the United States, with the remaining sites in Poland, South Korea, Russia, Thailand, Philippines, Canada, Hungary, and Turkey.

Patients were randomized to 1 of 3 treatment groups in a 1:1:1 ratio: Botox 3 U/kg (maximum dose of 100 U), Botox 6 U/kg (maximum dose of 200 U) or volume-matched placebo. Randomization was stratified based on 3 factors: 1) age (≤ 6 years and > 6 years), 2) designated principal muscle group (elbow flexors and wrist flexors), and 3) baseline (Day 1) modified Ashworth Scale (MAS) score of the principal muscle group MAS ≤2 and MAS >2).

There were no meaningful differences in the demographic features of the study participants in the modified intent-to-treat population (mITT) between the treatment groups. The mean age was 7.9 years, with 56 % of patients 6 years of age or older. Fifty-nine percent of the population was male, 62 % White, and 28% Asian. Thirteen percent of the mITT population had spasticity secondary to stroke. Most (79%) patients had hemiplegia.

Patients had either the elbow flexors or the wrist flexors designated as the principal muscle group (PMG) for analysis purposes. The PMG was required to have a MAS score ≥ 2 at baseline. If wrist flexors were identified as the PMG, finger flexors were also required to have a MAS score ≥ 1 at baseline. The elbow flexors were the PMG in 62% of the patients and the wrist flexors were PMG in 38% of patients.

The Modified Ashworth Scale (MAS) is a 6-point scale that ranges for 0 (no increase in muscle tone) to 5 (affected part(s) rigid in flexion or extension). The Clinical Global Impression of Overall Change (CGI) by Physician is a 9-point Likert scale ranging from -4 (very marked worsening) to +4 (very marked improvement).

Coprimary endpoints

The co-primary endpoints were:

- The average change from baseline in MAS score of the PMG at Weeks 4 and 6
- The average CGI assessed by a Physician at Weeks 4 and 6

The analysis of the coprimary endpoints used a mixed model repeated measures (MMRM) that included the baseline MAS score as the covariate, and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure. The physician-rated CGI was analyzed using an MMRM with similar factors and covariates. The applicant used a Hochberg procedure to control the family-wise type I error rate.

The Hochberg procedure to control the family-wise type I error rate was defined in the statistical analysis plan as the following:

p11: p value for Botox 6 U/kg vs placebo comparing MAS

p12: p value for Botox 3 U/kg vs placebo comparing MAS
p21: p value for Botox 6 U/kg vs placebo comparing CGI
p22: p value for Botox 3 U/kg vs placebo comparing CGI
p1 = max(p11, p21)
p2 = max(p12, p22)

The SAP also pre-specified the following decision rule:

Step 1: If p(2) ≤ 0.05, both doses are considered efficacious; otherwise go to step 2.
Step 2: If p(1) ≤ 0.025, its corresponding dose is considered efficacious; otherwise go to step 3.
Step 3: Neither dose is considered efficacious.

The details of the Hochberg procedure are discussed in Dr. Zhang's statistical review.

Efficacy results

The efficacy results for the co-primary endpoint are shown in tables 2 and 3. The results show a nominally positive result on the MAS, with a small p-value (<0.001) for both doses of Botox compared to placebo. However, the results for the CGI numerically favored both doses of Botox over placebo, but the contrasts did not reach statistical significance.

Table 2. Study 101 primary analysis of MAS (mITT population)

		BOTOX		
Visit	*Statistic*	*6 U/kg (N = 77)*	*3 U/kg (N = 78)*	*Placebo (N = 79)*
Baseline	n	77	78	79
	Mean ± SD	3.3 ± 0.45	3.3 ± 0.45	3.3 ± 0.44
Weeks 4 & 6	n	74	76	75
	Mean ± SD	1.4 ± 1.01	1.4 ± 0.98	2.1 ± 0.90
	Mean Change from Baseline ± SD	-1.9 ± 0.98	-1.9 ± 0.97	-1.2 ± 0.85
	LS Mean Change from Baseline (SE)	-1.87 (0.102)	-1.92 (0.101)	-1.21 (0.102)
	Difference (SE)	-0.66 (0.142)	-0.71 (0.143)	
	95% CI	(-0.938, -0.379)	(-0.992, -0.426)	
	P-value [a]	< 0.001	< 0.001	

CI = confidence interval; LS = least squares; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; MMRM = Mixed Model Repeated Measures; SD = standard deviation; SE = standard error

[a] P-values and 95% confidence intervals for between-group comparisons were obtained from a MMRM model including baseline MAS-B score as a covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age group, elbow flexors and wrist flexors for designated principal muscle group). Estimated differences are based on the least-square means.

Table 3. Study 101 primary analysis of CGI by physician (mITT population)

Visit	Statistic	BOTOX 6 U/kg (N = 77)	BOTOX 3 U/kg (N = 78)	Placebo (N = 79)
Weeks 4 & 6	n	74	76	75
	Mean ± SD	2.0 ± 1.01	1.9 ± 1.07	1.7 ± 1.12
	LS Mean (SE)	1.87 (0.108)	1.88 (0.108)	1.66 (0.108)
	Difference (SE)	0.21 (0.150)	0.22 (0.153)	
	95% CI	(-0.082, 0.511)	(-0.079, 0.523)	
	P-value [a]	0.155	0.147	

CGI = Clinical Global Impression of Overall Change; CI = confidence interval; LS = least squares; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; MMRM = Mixed Model Repeated Measures; SD = standard deviation; SE = standard error

[a] P-values and 95% confidence intervals for between-group comparisons were obtained from a MMRM model including baseline MAS-B score as a covariate and factors of age group, principal muscle group, treatment group, visit, treatment-by-visit interaction, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age group, elbow flexors and wrist flexors for designated principal muscle group). Estimated differences are based on the least-square means.

As the purpose of the CGI in the trial was to confirm the clinical meaningfulness of the change on MAS, and as results for that endpoint did not reach statistical significance, it was important to assess whether the proportion of patients with clearly clinically meaningful changes on the MAS was greater for patients treated with Botox than for patients on placebo. The proportion of patients with at least a one-point improvement on the MAS (Table 4) has been used in similar situations to support the clinical meaningfulness of the changes.[1] As illustrated in Table 4, these analyses show a greater proportion of responders in patients treated with either dose of Botox, and support the clinical meaningfulness of the observed changes in muscle tome.

Table 4. MAS Score of the Principal Muscle Group (PMG): Responders with at Least a 1-Grade Reduction from Baseline (Observed Data, mITT Population)

Visit Week	Statistic	BOTOX 6 U/kg (N = 77) n/N (%)	BOTOX 3 U/kg (N = 78) n/N (%)	Placebo (N = 79) n/N (%)
2	Responders	62/77 (80.5)	69/78 (88.5)	55/77 (71.4)
	P-value vs placebo [a]	0.140	0.004	
4	Responders	70/77 (90.9)	67/76 (88.2)	58/78 (74.4)
	P-value vs placebo [a]	0.002	0.008	
6	Responders	64/74 (86.5)	70/78 (89.7)	56/76 (73.7)
	P-value vs placebo [a]	0.031	0.007	
8	Responders	70/77 (90.9)	72/77 (93.5)	58/78 (74.4)
	P-value vs placebo [a]	0.002	< 0.001	
12	Responders	49/75 (65.3)	58/78 (74.4)	44/79 (55.7)
	P-value vs placebo [a]	0.293	0.024	

MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; N = number of participants assessed at that visit; n = number of responders

[a] P-values are based on logistic regression model with baseline MAS-B as a covariate and factors of age group, principal muscle group, treatment group, study center, and previous botulinum toxin exposure where age group and principal muscle group are represented by stratification categories (≤ 6 years and > 6 years for age group, elbow flexors and wrist flexors for designated principal muscle group).

— Source: Table 14.2-4

[1] Rychlik, R., Kreimendahl, F., Schnur, N., Lambert-Baumann, J., & Dressler, D. (2016). Quality of life and costs of spasticity treatment in German stroke patients. *Health economics review*, *6*(1), 27.

Secondary endpoints

The finger flexor muscle group was analyzed as a secondary endpoint using the subgroup of patients in whom the wrist was identified as the PMG. The average grade change from baseline score was compared to average of Week 4 and 6 scores on the MAS using an ANCOVA model. The results were numerically better for both doses of Botox compared to placebo, but did not reach statistical significance (Table 5). The effect size, however, was similar to that observed for the primary endpoint in the overall population, and the sample size for that group was less than half that of the overall population, limiting the power for that analysis.

Table 5. MAS-B Score of finger flexor muscle change from baseline by visit (ANCOVA using observed data, mITT Population)

		BOTOX		
Visit	*Statistic*	*6 U/kg (N = 29)*	*3 U/kg (N = 30)*	*Placebo (N = 31)*
Baseline	n	29	30	31
	Mean ± SD	2.7 ± 0.77	2.5 ± 0.73	2.7 ± 0.82
Week 4 & 6	n	28	30	29
	Mean ± SD	1.3 ± 1.07	1.1 ± 0.81	1.8 ± 0.98
	Mean Change from Baseline ± SD	-1.3 ± 0.98	-1.4 ± 1.13	-1.0 ± 0.89
	LS Mean Change from Baseline (SE)	-1.41 (0.184)	-1.46 (0.169)	-1.02 (0.170)
	Difference (SE)	-0.39 (0.239)	-0.44 (0.247)	
	95% CI	(-0.861, 0.091)	(-0.933, 0.051)	
	P-value [a]	0.111	0.078	

The Goal Attainment Scale (GAS) was assessed by the investigator or therapist. Two functional goals, one active and one passive, were selected by the participant and family in consultation with the physician investigator and/or treating physical therapist prior to treatment. The GAS was a 6-point scale from -3 (worse than start) to +2 (much more than expected). The results of the GAS did not show that patients were more likely to attain their preselected goals (active or passive) after treatment with 3- or 6-U/kg of Botox.

The Modified Tardieu Scale (MTS) was used to determine the passive range of movement at different movement velocities, as slow as possible (V1), and as fast as possible (V3), with the relative difference between a slow and a fast velocity passive stretch determining the dynamic component of the muscle contracture. At each visit, the same investigator (when possible) measured 2 joint angles by goniometer: the R1 angle, which was the "angle of catch" after a V3 stretch, and the R2 angle, which was defined as the passive joint range of movement following a V1 stretch. The results for the change from baseline for the angle of catch following a fast velocity stretch (R1) on the Tardieu Scale found the high and low dose of Botox were better than placebo at each visit, with nominally significant results for the average score for Week 4 and 6.

Additional Analyses

The applicant conducted additional analyses including the change from baseline for each PMG. Botox 3 U/kg and 6 U/kg were nominally better than placebo at Week 4 and 6 for both muscle groups in that analysis (Table 6). The least squares mean change from baseline for placebo was unusually large across all PMG.

Table 6. The MAS-B Score of the principal muscle group change from baseline to the average of weeks 4 and 6 (MMRM, Observed Data, mITT Population)

		Elbow Principal Muscle Group			Wrist Principal Muscle Group		
		BOTOX			BOTOX		
Visit	*Statistic*	*6 U/kg (N = 48)*	*3 U/kg (N = 48)*	*Placebo (N = 48)*	*6 U/kg (N = 29)*	*3 U/kg (N = 30)*	*Placebo (N = 31)*
Baseline	n	48	48	48	29	30	31
	Mean ± SD	3.3 ± 0.48	3.3 ± 0.47	3.3 ± 0.47	3.2 ± 0.41	3.2 ± 0.41	3.2 ± 0.40
Week 4 & 6	n	46	46	46	28	30	29
	LS Mean change from baseline (SE)	-1.99 (0.126)	-1.89 (0.126)	-1.28 (0.128)	-1.76 (0.196)	-1.96 (0.184)	-1.16 (0.181)
	P-value [b]	< 0.001	< 0.001		0.023	0.003	

LS = least squares; MAS-B = Modified Ashworth Scale - Bohannon; mITT = modified intent-to-treat; MMRM = Mixed Model Repeated Measures; SE = standard error

[a] P-values for between-group comparisons were obtained from a MMRM model including baseline MAS-B score as a covariate and factors of principal muscle group, visit, treatment -by-visit interaction, study center and previous botulinum toxin exposure where principal muscle group is represented by stratification categories (elbow flexors and wrist flexors).
Source: Modified from the Table 11-17 Applicants' CSR

The results for the Faces Pain Scale – Revised (Patients Age 4 years and Older), the Patient-reported Onset of Spasticity Symptom Relief, Quality of Upper Extremity Skills Test, and the Patient-reported Benefit of Injection were not nominally better for either Botox groups than for placebo. There were fewer patients in Quality of Upper Extremity Skills Test included in the analyses of these endpoints, and the failure to show a difference from placebo may have been related to an insufficient sample size.

Subgroup analyses
Dr. Zhang found that patients in the U.S. with upper limb spasticity had little response on the CGI to treatment with Botox, but that group was small, making conclusions difficult. There were no other meaningful differences in the subgroups (e.g., age, sex, or race) with regards to the benefit of Botox for treatment of upper limb spasticity assessed using the co-primary endpoints.

Efficacy conclusion for upper limb spasticity
Dr. Zhang did not find that either dose of Botox was statistically different from placebo. Her conclusion was primarily because the difference from baseline to Week 4 and 6 on the physician-rated CGI did not reach statistical significance under the Hochberg procedure to control the Type I error. However, the benefit of both doses of Botox (3 U/kg and 6 U/kg) is supported by the nominally highly statistically significant difference from baseline on the MAS scale between both doses of Botox and placebo, and by the greater proportion of patients with at least a 1-point change from baseline on the MAS-B for both doses of Botox, compared with placebo. That degree of change is clearly meaningful.

5. Safety

The long-term, open-label safety information comes from the extension studies 191622-105 (upper limb spasticity) and 191622-112 (lower limb spasticity). (b) (4)

[redacted]

[redacted] (b) (4)

In open-label studies 105 and 112, patients could receive up to 5 treatments every 12 weeks over 60 weeks of follow-up visits. Patients who completed studies 101 and 111 [redacted] (b) (4) were eligible to participate in studies 105 (upper limb) or 112 (lower limb), respectively. In addition, both open-label studies could enroll de novo patients who did not participate in either controlled study. In studies 105 and 112, the maximum dose was also increased up to 10 U/kg (maximum 340 U total) in any combination of 3 limbs in study 105, and any combination of limbs in study 112.

Exposure

One-hundred-twelve patients received 4 treatment with doses of Botox (100 U-200 U) proposed for labeling for one year, with 24 patients treated with at least 200 U (total dose) every 12 to 14 weeks for 4 consecutive treatments. Sixty-three patients received the highest dose (8 U/kg- maximum of 300 U) for 4 consecutive treatments (every 12-14 weeks) for 1 year. The exposure to treatment of pediatric spasticity exceeds the minimum number of patients in the pre-submission agreement with FDA and fulfills the minimum exposure included in the postmarketing requirement to study pediatric spasticity. The 120-Day safety update included 123 patients who received at least 2 treatments and 35 patients who received at least 4 treatments with 10 U/kg or a maximum of 340 U (total dose) of Botox administered in any combination of limbs for treatment of pediatric spasticity.

Discontinuation

In Study 101, 6 patients withdrew from the study. A single patient randomized to Botox 6 U/kg withdrew because of an adverse event of stomatitis. In Study 111, 8 patients withdrew early, but no patient withdrew because of an adverse event. In Study 105, 27 patients discontinued early. Most (27) withdrew consent (17), but no patient withdrew because of an adverse event. In Study 112, up to the 120-day safety update cutoff date, 6 patients withdrew prematurely (376 completed patients), but no patient withdrew early because of an adverse event.

Serious adverse events

There were no deaths reported during studies 101, 111, or their open-label extension studies. Eleven patients experienced a serious adverse event (SAE) during studies 101 or 111. Dr. Goldstein concluded that none of the SAEs were related to study treatment. In the open-label studies, 437 patients reported 47 SAEs. Seizure (13 patients) was the most commonly reported, with pneumonia (5), pharyngitis (4), hemiplegia (3) and bronchitis (2) as the only events reported in 2 or more patients.

All adverse reactions

Tables 7 and 8 list all adverse events that were reported in at least 2% of patients and were more frequent than on placebo in studies 101 and 111. Respiratory tract infection was the most frequently reported adverse reaction in patients treated for upper limb spasticity. Two patients treated with Botox experienced a first-time seizure. Attribution to drug is unlikely.

Table 7. Adverse Reactions in Study 101 (Upper Limb Spasticity) with an incidence ≥2% and Higher than Placebo

Adverse Reactions	Preferred Term	Botox 3 U/kg N=78 %	Botox 6 U/kg N=77 %	Placebo N=79 %
Infections and infestations	Upper respiratory tract infection	5	9	3
Infections and infestations	Viral upper respiratory tract infection	5	8	6
Infections and infestations	Rhinitis	4	0	1
General disorders and administration site conditions	Injection site pain	3	4	1
Gastrointestinal disorders	Constipation	0	3	1
Gastrointestinal disorders	Diarrhoea	4	0	1
Gastrointestinal disorders	Nausea	0	4	0
Musculoskeletal and connective tissue disorders	Muscular weakness	4	1	1
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	0	4	1
Nervous system disorders	Seizure	1	3	0
Nervous system disorders	Partial seizures	0	3	0
Respiratory, thoracic and mediastinal disorders	Nasal congestion	0	3	1
Injury, poisoning and procedural complications	Ligament sprain	3	0	1

A similar pattern of infectious diseases and symptoms related to infectious diseases was observed in Study 111 (table 8). The difference in incidence between Botox and placebo was very small.

Table 8. Adverse Reactions in Study 111 (Lower Limb Spasticity) with an incidence ≥2% and Higher than Placebo

Adverse Reactions System Organ Class (SOC)	Preferred Term	Botox 4 U N=126 %	Botox 8 U N=128 %	Placebo N=128 %
Infections and infestations	Upper respiratory tract infection	8	6	7
General disorders and administration site conditions	Pyrexia	6	4	5
Respiratory, thoracic and mediastinal disorders	Cough	5	3	2
General disorders and administration site conditions	Injection site pain	2	2	0
Infections and infestations	Tonsillitis	2	2	1
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain	0	2	1
Gastrointestinal disorders	Dental caries	0	2	1
General disorders and administration site conditions	Injection site erythema	0	2	0
Infections and infestations	Varicella	0	2	0
Injury, poisoning and procedural complications	Ligament sprain	1	2	0
Injury, poisoning and procedural complications	Skin abrasion	0	2	0

Adverse Reactions System Organ Class (SOC)	Preferred Term	Botox 4 U N=126 %	Botox 8 U N=128 %	Placebo N=128 %
Metabolism and nutrition disorders	Decreased appetite	0	2	0
Gastrointestinal disorders	Diarrhoea	3	1	2
Infections and infestations	Pharyngitis	4	1	0

Adverse reactions in pooled open-label studies 105 and 112
A table presenting adverse reactions in pooled open-label studies 105 and 112 is included in Dr. Goldstein's review. The most common adverse reactions in pooled open-label studies were pharyngitis, headache, and vomiting (12% each). All three adverse reactions were most common in the low dose range (<4.5 U/kg) in patients treated for upper limb spasticity. The adverse events reported in the open-label studies do not raise new safety concerns.

Analysis of spread of toxin adverse events
There were no clear cases that represented potential distant or local spread of toxin related adverse events in patients treated with Botox. The reported potential cases included only isolated symptoms of constipation or focal weakness.

Clinical laboratory testing
There was no clinical meaningful change in chemistry, electrolytes, or hematology analytes during the studies.

Safety Conclusions
The pattern and frequency of adverse reaction in the studies supporting both supplements did not reveal new safety concerns. The exposure in the submitted clinical studies was adequate and fulfilled the postmarketing requirement. There were no convincing cases of potential distant spread of toxin related adverse events.

6. Pediatrics

The following postmarketing commitment and requirements are fulfilled by supplement S-5309:

Postmarketing commitment:

1. Postmarketing Commitment-2607-4 Randomized, double-blind, adequately controlled, multiple fixed dose, parallel group clinical trial of Botox (onabotulinumtoxinA) in botulinum toxin-naïve children age 2-17 years with upper extremity spasticity. The minimum duration of the trial should be 12 weeks. The protocol for the trial should be submitted to the FDA as a special protocol assessment (SPA).

Postmarketing requirements:

1. PREA Postmarketing Requirement #2342-1 that requires a juvenile rat toxicology study.

2. Deferred pediatric long-term safety study (minimum 12 months) under PREA for the treatment of upper limb spasticity in pediatric patients ages 2 years through 16 years 11 months. The doses evaluated must be at least as high as those shown effective in the pediatric efficacy study (PMR #2342-2), or those commonly used to treat upper limb spasticity in pediatric patients, if an effective dose is not identified in the pediatric efficacy study (PMR #2342-2). The study must assess distant spread of toxin effects, and the effects of Botox on blood glucose and alkaline phosphatase. The study report must include safety information on at least 300 patients who received 2 injections over a 6-month period, with at least 100 patients who received 4 injections over a 12-month period, with at least 60 patients who received the highest recommended dose (if any).

7. Other Relevant Regulatory Issues

Two investigators and one sub-investigator in Study 101 received study grants from the applicant that exceeded the reporting threshold. The sub-investigators also performed study-related assessments in studies 111 and 112. None of the individuals were able to influence the outcome of the respective clinical studies.

Clinical site inspections were not requested for this application because most of the sites were small, and excluding individual sites in the analyses would not change the efficacy results.

8. Labeling

Agreement was reached with the sponsor regarding labeling changes for the treatment of upper limb spasticity.

9. Recommendations/Risk Benefit Assessment

The efficacy of Botox for the treatment of upper spasticity in children 2 to 17 years old was clearly established using endpoints for which the division has considerable experience. The meaningfulness of muscle tone changes was established by physician-

rated CGI results and/or by the proportion of patients with at least a 1-point change on the MAS scale. The 300 U maximum dose recommended in the label is not associated with new safety concerns in children up to 17-years-old.

Although most patients in the studies of Botox for pediatric spasticity had cerebral palsy, some patients with upper limb spasticity had spasticity caused by stroke. As the site and mechanism of action of botulinum toxins (including Botox), which interfere with the release of acetylcholine into the synapse at the neuromuscular junction, are well understood, the data support a broad indication for the treatment of upper spasticity in pediatric patients 2 to 17 years of age, with no limitation based on the cause of spasticity.

Supplement S-5309 for the treatment of upper limb spasticity will be approved.

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