Summary Review

Date	9/24/2019
From	Gerald D. Podskalny, DO, MPHS Eric Bastings, MD
Subject	Summary Review
NDA/BLA # Supplement#	BLA 125274 (S-115)
Applicant	Ipsen Biopharm Ltd
Date of Submission	3/25/2019
PDUFA Goal Date	09/25/2019
Proprietary Name / Established (USAN) names	Dysport (abobotulinumtoxinA)
Dosage forms / Strength	Sterile 300 Unit and 500 Unit vials for injection
Proposed Indication(s)	Pediatric Upper Limb Spasticity
Action	**Approval**

1. Background

Dysport (abobotulinumtoxinA) was first approved on April 29, 2009, for the treatment of cervical dystonia, and for the temporary improvement in the appearance of moderate to severe glabellar lines in adult patients under 65 years of age. FDA approved efficacy supplements that added indications for the treatment of spasticity in adult patients on July 15, 2015, and for the treatment of lower limb spasticity in pediatric patients 2 years of age and older on July 29, 2016.

Ipsen (applicant) submitted efficacy supplement S-115 in support of a new indication for the treatment of pediatric upper limb spasticity in children ages 2 to 17 years. The supplement is also intended to fulfill PMC 2933-2 (goal date February 26, 2019) and Safety PMR 2564-5.

The supplement was filed with Priority Review status because there was no approved treatment for pediatric upper limb spasticity when the application was filed.

The review team is described in Table 1.

Table 1. Review Team

Review Discipline/Division	Reviewer
Clinical Review/ Division of Neurology Products	Susanne Goldstein Gerald D. Podskalny
Statistics Review/Division of Biometrics I	Ququan Liu Kun Jin Hsien Ming Hung
Labeling Review/ Division of Medication Error Prevention and Analysis	Colleen Little Briana Rider
Patient Labeling Review/ Division of Medical Policy Programs	Sharon W. Williams, Shawna Hutchins LaShawn Griffiths,
Package Insert and Medication Guide Review/ Office of Prescription Drug Promotion	Dhara Shah Aline Moukhtara

Reference ID: 4497056

2. Clinical/Statistical- Efficacy

The primary evidence for effectiveness is supported by the results of the first treatment cycle of Study Y-55-52120-153 (referred to as Study 153).

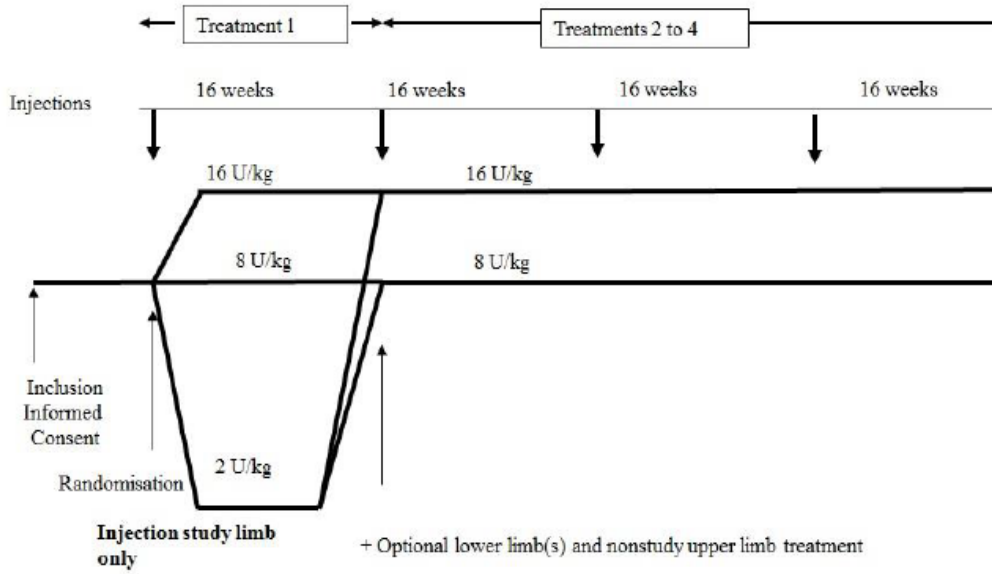
Study Y-55-52120-153

Ququan Liu, M.D., M.S., was the primary statistical reviewer for this BLA supplement.

Study 153 was a multicenter study assessing the efficacy and safety of Dysport for the treatment of spasticity caused by cerebral palsy (CP) in children 2 to 17 years of age. The study included four treatment cycles. During treatment cycle 1 (TC 1), patients were randomized 1:1:1 in a double-blinded fashion to receive Dysport 16 U/kg, Dysport 8 U/kg or Dysport 2 U/kg (see Figure 1). Information from treatment cycles 2 to 4 was used to support the long-term safety of Dysport for the proposed indication, and is discussed later in this document.

The primary efficacy analysis compared the 8 U/kg (maximum of 320 U) and 16 U/kg (maximum of 640 U) dosages of Dysport with the 2 U/kg dosage (see Figure 1). Enrollment was stratified based on age (2 to 9 years and 10 to 17 years) and on whether patients were botulinum toxin naïve or non-naïve at baseline.

Figure 1. Study Design



Source=Completed study report

In TC 1, patients were treated with study medication on Day 1, with follow-up visits scheduled at Weeks 2, 4, 6, 12 and 16. At study entry, the site investigator identified a primary targeted muscle group (PTMG), which could be either the elbow flexors or the wrist flexors, in a single upper limb. The doses for the primary targeted muscle groups are listed in Table 2.

Table 2. Dose of Dysport Administered in the Primary Targeted Muscle Groups in Treatment Cycle 1 of Study 153

Muscle Group	Injection Volume (mL)	Number of Injection Sites	Dose per Muscle in U/kg (Maximum U)		
			Control Group	Treatment Groups	
			Dysport 2 U/kg	Dysport 8 U/kg [a]	Dysport 16 U/kg [a]
Elbow Flexors					
Brachialis	0.6	2	0.75 U/kg (30 U)	3 U/kg (120 U)	6 U/kg (240 U)
Brachioradialis	0.3	1	0.375 U/kg (15 U)	1.5 U/kg (60 U)	3 U/kg (120 U)
Wrist Flexors					
Flexor carpi radialis	0.4	1 to 2	0.5 U/kg (20 U)	2 U/kg (80 U)	4 U/kg (160 U)
Flexor carpi ulnaris	0.3	1	0.375 U/kg (15 U)	1.5 U/kg (60 U)	3 U/kg (120 U)

Source=Completed study report

At the Week 16 visit, patients were assessed for possible re-treatment. People who were not deemed eligible for reinjection at that time were thereafter seen every 6 weeks (± 2 weeks) until they were eligible for re-treatment. The minimum re-treatment interval was every 16 weeks. To maintain the study blind, Dysport was reconstituted by an independent pharmacist or nurse to ensure that syringes for each dose level had the same volume.

For all treatment cycles, additional muscles in the study upper limb (SUL) could be injected. These additional muscles were selected by the investigator. For treatment cycle 2, 3 and 4, injection into the lower limbs and the non-study upper limb (nonSUL) were allowed at the same time as SUL injection.

In treatment cycles 2 to 4, eligible patients received up to 3 additional treatments with Dysport 8 U/kg or 16 U/kg in the SUL, but patients and investigators remained blinded to the Dysport dosage. Patients randomized to receive 8 U/kg or 16 U/kg were to remain on their randomized dose of Dysport, but a dosage reduction or increase was possible based on the investigator's judgment. Patients who were randomized to 2 U/kg in TC 1 were re-randomized to 8 U/kg or 16 U/kg in cycles 2 to 4. The maximum dose when both upper limbs were injected was 21 U/kg (up to 840 U), and 30 U/kg or 1000 U (whichever was lower) when both upper limbs and lower limbs were injected. All subjects whose first three treatment intervals fell between ≥16 and ≤22 weeks received four treatments and exited the study as soon as a new injection was required and no later than 22 weeks after last injection All other subjects were not to be given any further study treatment after Week 52 and exited the study after 16 weeks of follow-up after the last treatment.

Pre-study physiotherapy, occupational therapy, or use of splints and/or orthoses were initiated at least 30 days prior to the baseline visit for TC 1 and patients were to continue the therapy up to Week 16 following TC 1.

Demographic Characteristics

The mean age of patients in the mITT population was 9 years. Fifty-seven percent of patients were in the 2 to 9 years of age group, with even distribution in all study arms. The majority of patients were male (60%) and 75% of the study population was White. Thirty percent of patients were from the United States. Eighty-six percent of patients received physical or

occupational therapy throughout TC 1, and 31% of patients were naïve to botulinum toxin treatment; this was similar in all study arms.

Patient Disposition
Ten patients withdrew prematurely during TC 1; an additional 22 patients completed TC 1 but did not enter TC 2. Another 63 patients completed TC 2, and 43 TC 3, leaving only 55 patients who entered TC 4. Two patients withdrew for adverse events in TC 1 and TC 2, and one patient in TC 3. No patients withdrew in TC 4 because of an adverse event.

Efficacy Endpoints
The primary efficacy endpoint was the least square (LS) mean change from baseline in Modified Ashworth Scale (MAS) for the primary targeted muscle group (PTMG) in the SUL.

The Modified Ashworth Scale (MAS) is a 6-point scale ranging from 0 (no increase in tone) to 4 (affected parts rigid in flexion or extension).

0: No increase in muscle tone.
1: Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion when the affected part is moved in flexion or extension.
2: Slight increase in muscle tone, manifested by a catch followed by minimal resistance throughout the remainder (less than half) of the range of motion.
3: More marked increase in muscle tone through most of the range of motion, but affected part(s) easily moved.
4: Considerable increase in muscle tone, passive movement difficult.
5: Affected part(s) rigid in flexion or extension.

An independent investigator (different from the one who assessed the PGA) performed the assessment of the MAS.

<u>First secondary endpoint: Physician's Global Assessment of the Treatment Response</u>
Physician Global Assessment (PGA) of treatment response for TC 1 was assessed by asking the investigator the following question: 'how would you rate the response to treatment in the subject's lower limb(s) since the last injection?'

Answers were made on a 9-point rating scale (-4: markedly worse, -3: much worse -2: worse, -1: slightly worse, 0: no change, +1: slightly improved, +2: improved, +3: much improved, +4: markedly improved).

<u>Second secondary endpoint: Goal Attainment Scale</u>
The Goal Attainment Scale (GAS) for TC 1 was used to measure progress towards individual therapy goals. Individual goals were defined for each patient by the physician, with the child's parents/guardians, prior to each treatment. The score for each goal was based on whether the subject has reached the predetermined level of achievement set out at the baseline and subsequent treatment visits.

Tertiary Endpoints
The applicant designated 17 tertiary endpoints, but the testing procedure stopped under the hierarchy before any of the tertiary endpoints was tested.

Statistical Methodology for the Efficacy Analyses
In order to control the family-wise type I error rate, a 4-step hierarchical testing procedure was applied, whereby a p-value lower than 0.05 had to be attained at each step, in order to proceed to the following step; otherwise, the procedure was stopped.

The sequence for testing Dysport versus placebo was as follows:

- Step 1: Dysport 16 U/kg versus 2 U/kg for the primary efficacy endpoint.
- Step 2: Dysport 16 U/kg versus 2 U/kg for the first secondary efficacy endpoint.
- Step 3: Dysport 8 U/kg versus 2 U/kg for the primary efficacy endpoint.
- Step 4: Dysport 8 U/kg versus 2 U/kg for the first secondary efficacy endpoint.

Superiority of Dysport 16 U/kg over Dysport 2 U/kg was to be considered demonstrated if the p-values associated with the step 1 and step 2 comparisons were <0.05; superiority for the 8 U/kg dosage over the 2 U/kg dosage was to be considered demonstrated if the p-values associated with the step 3 and step 4 comparisons were <0.05.

Analysis Plan
For the primary endpoint, the applicant selected an analysis of covariance (ANCOVA) on the rank of the mean change from baseline to Week 6 on the MAS, with the treatment group, baseline value, the two stratification factors (age range and botulinum treatment naïve status at baseline) and the pooled center as fixed effects in the model. The efficacy analysis was to be performed on the mITT population, defined as all randomized patients who received at least one injection of the study treatment at the patient's randomized dose and had a MAS score in the PTMG assessed both at baseline and at TC 1 (Week 6).

The analysis of the secondary endpoints was to be performed with an analysis of variance (ANOVA) using the rank of the mean PGA score with the treatment group, the two stratification factors and the pooled center as fixed effects.

Efficacy Results
Dr. Liu independently confirmed the applicant's primary endpoint results, as displayed in Table 3. The Least Means (LS) mean square difference for the ranked change in MAS from baseline to Week 6 between the Dysport 2 U/kg group and the Dysport 8 U/kg and 16 U/kg groups was statistically significant, with evidence of dose-response.

Reference ID: 4497056

Table 3. Change from Baseline to Week 6 in Modified Ashworth Scale Score (Treatment Cycle 1 -mITT Population)

	Control Group	Treatment Groups	
Visit Statistic	**Dysport 2 U/kg (N=69)**	**Dysport 8 U/kg (N=69)**	**Dysport 16 U/kg (N=70)**
Baseline	**n=69**	**n=69**	**n=70**
Mean (SD)	3.1 (0.3)	3.1 (0.3)	3.1 (0.5)
Week 6 (primary timepoint)	**n=69**	**n=69**	**n=70**
Mean (SD)	1.6 (1.0)	1.2 (1.0)	0.9 (0.9)
Mean change (SD)	-1.5 (1.1)	-1.9 (1.0)	-2.2 (0.9)
LS mean of ranked change from baseline values (SE) (95% CI)	125.8 (6.6) (112.7, 138.9)	102.5 (6.6) (89.5, 115.6)	85.4 (6.6) (72.3, 98.5)
LS mean of back transformed change from baseline values	-1.6	-2.0	-2.3
Difference in LS means back transformed		-0.4	-0.7
p-value [a]		0.0118	<0.0001

[a]: p-value based on ANCOVA on the ranked changes from baseline including treatment group, the baseline value, the two stratification factors (age range and botulinum toxin treatment-naïve status at baseline) and the pooled center as fixed effects. Source: FDA Statistical Review

Dr. Liu reviewed the applicant's sensitivity analyses, including a proportional odds model and baseline observation carried forward analysis on all randomized subjects. Both sensitivity analyses were consistent with the primary analysis.

The Physician's Global Assessment (PGA) at the Week 6 visit was not significantly different between the Dysport 2 U/kg group and the Dysport 8 U/kg and 16 U /kg groups (see Table 4). It is important to remember, however, that all 3 groups received active drug, and that the low dose group (2 U/kg), which served as control, may have derived a therapeutic benefit.

Table 4. Physician Global Assessment of Treatment Response at Week 6 (Treatment Cycle 1) by Study Limb Dose (mITT Population)

	Control Group	Treatment Groups	
Visit Statistic	**Dysport 2 U/kg (N=69)**	**Dysport 8 U/kg (N=69)**	**Dysport 16 U/kg (N=70)**
Week 6 (primary timepoint)	**n=68**	**n=69**	**n=70**
Mean score (SD)	1.7 (0.9)	2.0 (0.9)	2.0 (0.9)
LS mean of ranked score values (SE) (95% CI)	97.1 (7.1) (83.1, 111.0)	109.5 (7.0) (95.6, 123.4)	109.7 (7.1) (95.8, 123.7)
LS mean of back transformed score values	1.8	2.0	2.0
Difference in LS means scores back transformed		0.2	0.2
p-value		0.2043	0.1880

Source=Completed study report

Goal Attainment Scale

The proportion of patients who achieved their preselected functional goals was not significantly different between the Dysport 2 U/kg group and the Dysport 8 U/kg and 16 U/kg groups.

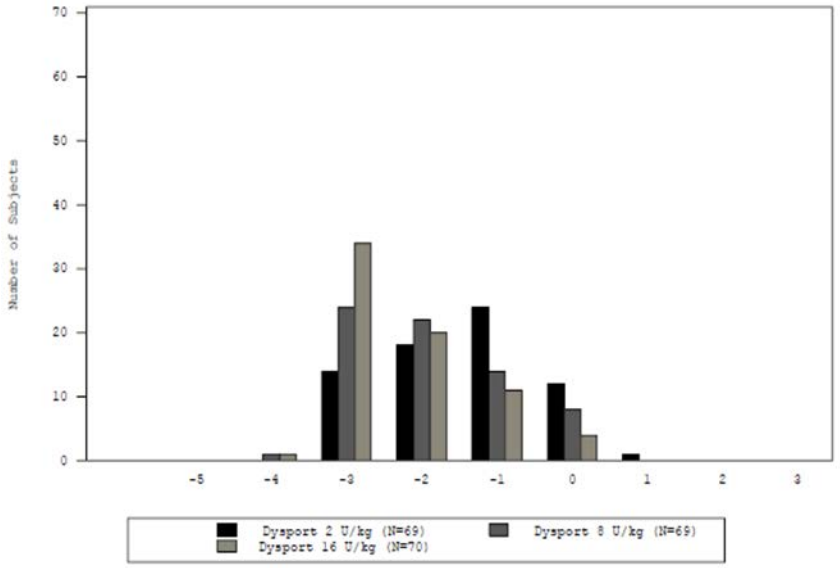
MAS Responder Rate

In order to assess the clinical meaningfulness of the primary endpoint results (in the context

of no statistically significant effect on the PGA), we also considered the distribution of patients with clearly meaningful changes in MAS scores (e.g., ≥1-point responders). As the applicant's regression model for the ≥1-point MAS responder analysis for the change from baseline to Week 6 in the MAS for the PTMG in the study upper limb did not converge, Dr. Liu performed a separate logistic regression analysis using a penalized likelihood method to correct the convergence failure and allow the logistic regression model for ≥1-point responders. The results showed that the 1-point MAS responder rate was nominally significantly higher for the Dysport 16 U/kg group (94.3%) than for the Dysport 2 U/kg group (81.2%) (OR=4.15, 95% CI (1.21, 14.29), nominal p-value = 0.024). That higher responder rate establishes the clinical meaningfulness of the MAS changes observed with Dysport 16 U/kg. The 1-point MAS responder rate in the Dysport 8 U/kg group (88.4%) was numerically higher than in the Dysport 2 U/kg group (OR=1.60, 95% CI (0.62, 4.10), but the contrast did not reach nominal significance (p-value=0.3276).

The distribution of MAS changes is displayed in Figure 2. The number of 1-point responders in the 2 U/kg group is greater than the number of responders in the 8 U/kg or the 16 U/kg, but the number of 2- and 3-point responders was greater in the Dysport 8 U/kg and 16 U/kg groups than in the 2 U/kg group (see Figure 2 and Table 5) . It is important to remember that the control group received a low dose of active drug, which may have provided a therapeutic benefit. In the absence of placebo, that benefit cannot be quantified.

Figure 2. Modified Ashworth Scale in the PTMG at Treatment Cycle 1 (Distribution of MAS categorical changes from Baseline at Week 6), by Study Limb Dose - mITT Population



Source: Completed Study Report

Reference ID: 4497056

Table 5. Responders based on the Modified Ashworth Scale Score in the PTMG (Treatment Cycle 1) by Study Limb Dose (mITT Population)

	Control Group	Treatment Groups	
Visit Statistic	**Dysport 2 U/kg (N=69)**	**Dysport 8 U/kg (N=69)**	**Dysport 16 U/kg (N=70)**
≥1-grade Reduction			
Week 6	**n=69**	**n=69**	**n=70**
Responders, n (%)	56 (81.2)	61 (88.4)	66 (94.3)
Logistic regression not performed since model did not converge			
≥2-grade Reduction			
Week 6	n=69	n=69	n=70
Responders, n (%)	32 (46.4)	47 (68.1)	55 (78.6)
Odds ratio vs Dysport 2 U/kg (95% CI)	-	2.4 (1.2, 5.0)	4.2 (2.0, 9.1)
p-value	-	0.0132	0.0002
p-value	-	0.4827	0.0283
≥3-grade Reduction			
Week 6	n=69	n=69	n=70
Responders, n (%)	14 (20.3)	25 (36.2)	35 (50.0)
Odds ratio vs Dysport 2 U/kg (95% CI)	-	2.4 (1.1,	4.2 (1.9,
p-value	-	0.0335	0.0003

Source=Completed study report

The same ANCOVA model was used to assess the change in MAS score from baseline to Week 6 of TC 1 for each PTMG. For elbow flexors, the change in MAS scores was nominally greater for Dysport 8 U/kg and 16 U/kg than for Dysport 2 U/kg (p-value = 0.0003 and <0.0001, respectively). For finger flexors, the change in MAS scores was nominally greater for Dysport 8 U/kg and 16 U/kg than for Dysport 2 U/kg (p-value = 0.0008 and = 0.0066, respectively). For wrist flexors, the change in MAS scores was nominally greater for Dysport 16 U/kg than for Dysport 2 U/kg (p-value 0.0295), but not nominally different between Dysport 8 U/kg and Dysport 2 U/kg (p=0.2521).

The results of Dr. Liu's analysis of subgroups using the primary endpoint show a numerical trend of greater improvement in the change in MAS score for the 16 U/kg group compared with the 8 U/kg treated group in all demographic subgroups.

Efficacy Conclusions:
Study 153 provides evidence of effectiveness for Dysport 16 U/kg for the treatment of upper limb spasticity in children ages 2 to 17 years old, based on the primary endpoint results and the distribution of patients with clinically meaningful changes in MAS scores (e.g., ≥1-point responders). The study also provides evidence that the 8 U/kg dosage may also provide clinical benefit to some patients. Therefore, a dosing range of 8 to 16 U/kg will be recommended in labeling, (b) (4)

3. Safety

Dr. Suzanne Goldstein was the primary clinical reviewer for this supplement.

Exposure
The safety population in Study 153 included 210 patients; of these, 40 patients received at least three consecutive injections of Dysport 16 U/kg within 54 weeks. Another 34 patients received three consecutive injections of Dysport 8 U/kg within 12 months. Additional long-term safety information from 21 patients treated in Study 147 (pediatric lower limb spasticity) was included; Study 147 was reviewed previously (pediatric lower limb spasticity supplement).

There is adequate exposure to support labeling recommendations and support the long-term safety of Dysport for the treatment of pediatric upper limb spasticity. The combined long-term exposure to Dysport for the treatment of pediatric upper limb and lower limb spasticity clinical programs fulfills the pediatric postmarketing requirement to study at least 100 patients treated for spasticity (half upper and half lower extremity) for one year.

Adverse Events

Serious Adverse Events
No patient died while participating in Study 153. In TC 1, 7 patients reported 8 non-fatal serious adverse events. Three patients in the 2 U/kg group, two patients in the 8 U/kg group, and two patients in the 16 U/kg group reported at least one serious adverse event.

The most frequently reported adverse event was seizure or epilepsy, with 2 events for each term. Thirteen of the 18 patients who reported at least one event of seizure/epilepsy had a history of epilepsy at baseline. None of the remaining serious adverse events appeared related to treatment with Dysport.

All Adverse Reactions
The most frequently reported adverse reactions in Study 153 were upper respiratory tract infection, pharyngitis, and muscular weakness (see Table 6).

Table 6. Incidence of Adverse Reactions in ≥ 3% and greater than 2 U/kg in Study 153

Adverse Reactions	DYSPORT 2 Units/kg[1] (N=70) %	DYSPORT 8 Units/kg (N=70) %	DYSPORT 16 Units/kg (N=70) %
Infections and infestations			
Upper respiratory tract infection	7	9	11
Influenza	1	1	3
Pharyngitis[2]	9	6	10
Gastrointestinal disorders			
Nausea	0	3	1
Musculoskeletal and connective tissue disorders			
Muscular weakness	1	4	6
Nervous system disorders			
Headache	0	6	3
Epilepsy	1	0	4

1 Low dose active comparator arm
2 Includes pharyngitis, pharyngitis streptococcal, pharyngotonsillitis

Reference ID: 4497056

Source=FDA

Adverse Events Leading to Discontinuation
Five patients discontinued from Study 153 because of an adverse event. None of these appear related to treatment with Dysport.

Adverse Events of Special Interest
Two patients had adverse events suggestive of spread of toxin. On further review of the narratives, neither patient had a presentation consistent with distant spread of toxin.

Eight patients experienced suspected hypersensitivity reactions that began a few hours to seven days after treatment. All of the events involved cutaneous reactions; one patient experienced urticaria, while the remaining patients experienced a skin rash. No case of anaphylaxis was reported.

Clinical Laboratory Monitoring
Complete blood counts were not tested during any phase of the study. Clinical chemistry, hemoglobin A1c and alkaline phosphatase (total and bone isoenzyme) were assessed during TC 1 at the baseline and end-of-study visits. No clinically relevant changes were observed in any of the assessed laboratory parameters.

Vital Signs and Electrocardiograms
There were no clinically relevant changes in blood pressure or pulse observed in patients during the study. There were no clinically relevant changes in electrographic parameters.

Safety Conclusions
Analysis of the controlled and long-term safety information in pediatric patients treated for upper limb spasticity found no new safety concerns. The ability to delay retreatment to 16-(b) (4) weeks in some patients will be reflected in the label.

4. Pediatrics

The FDA's Pediatric Research Committee (PeRC) concurred with the division's recommendation to consider the postmarketing commitment to study Dysport for the treatment of upper limb spasticity in pediatric patients and the postmarketing requirement to study the long-term treatment of spasticity in pediatric patients fulfilled.

5. Other Relevant Regulatory Issues

Financial Disclosures
The applicant certified that they did not enter into reportable financial relationship with clinical investigators who participated in the covered study. One investigator had received payment from Ipsen for her work in another therapeutic area. The FDA's office of Scientific Investigations inspected the investigator's clinical site and found no evidence of misconduct in the study records. The applicant also certified that they did not use in any capacity the services of any person debarred under 306 of Federal Food, Drug and Cosmetic Act in connection with this application.

Outstanding Regulatory Issues
None.

6. Labeling

Labeling recommendations from the agency's Division of Medication Error Prevention and Analysis and Office of Prescription Drug Promotion were included in the label.

7. Recommendations/Risk Benefit Assessment

Risk Benefit Assessment

The efficacy of Dysport for the treatment of upper limb spasticity in children 2 to 17 years of age was clearly established using endpoints for which the division has considerable experience. The meaningfulness of muscle tone changes was established by the proportion of patients with at meaningful change on the MAS scale. The 640 U maximum recommended dose proposed for the treatment of upper limb spasticity is not associated with any new safety concern in the pediatric population.

Although the pivotal efficacy study was conducted in patients with spasticity related to cerebral palsy, the good understanding of the pathophysiology of spasticity and of the site and mechanism of action of botulinum toxins (including Dysport), which interfere with the release of acetylcholine into the synapse at the neuromuscular junction, support a broad indication for the treatment of upper spasticity in pediatric patients 2 to 17 years of age. However, because of marketing exclusivity for another botulinum toxin product, the approved indication has to be restricted to the treatment of spasticity in pediatric patients 2 years of age and older, excluding spasticity caused by cerebral palsy.

Postmarketing Requirements and Commitments

Postmarketing Commitment 2933-2 is Fulfilled
A randomized, double-blind, adequately controlled, multiple fixed doses, parallel group clinical study of Dysport (abobotulinumtoxinA) in botulinum toxin-naive children age 2-17 years with upper extremity spasticity. The minimum duration of the study is 12 weeks. The study should be submitted to the FDA for special protocol assessment.

Postmarketing Requirement 2564-5 is Fulfilled
Submit safety data assessing distant spread of toxin effects after multiple administrations of Dysport (abobotulinumtoxinA), during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years) (approximately half upper, and half lower extremity spasticity). In addition, submit data assessing the effects of Dysport (abobotulinumtoxinA) on blood glucose and alkaline phosphatase as a marker of bone metabolism.

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/s/

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