CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125360

SUMMARY REVIEW

MEMORANDUM

DATE: July 25, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, BLA 125360

SUBJECT: Recommendation for action on BLA 125360, for the use of Xeomin (incabotulinumtoxinA) in patients with either Cervical Dystonia (CD) or Blepharospasm

BLA 125360, for the use of Xeomin (incabotulinumtoxinA) in patients with either Cervical Dystonia (CD) or Blepharospasm, was submitted on 7/2/09 by Merz Pharmaceuticals GmbH. (b) (4)

The current application contains the results of two adequate and well-controlled trials: one in patients with CD and one in patients with blepharospasm, as well as the requisite safety data and all other relevant data (non-clinical, chemistry and manufacturing, etc.).

The application has been reviewed by Dr. Kenneth Bergmann, clinical reviewer (efficacy for blepharospasm), Dr. Anne Constantino, clinical reviewer (efficacy for CD), Dr. Ohidul Siddiqui, statistician, Dr. Lisa Jones, clinical safety reviewer, Dr. Sally Hughes, safety team leader, Walter Fava, Division of Medication Error Prevention and Analysis (DMEPA), Dr. Kimberly Rains, Office of Biotechnology Products, Melissa Hulett, Division of Risk Management (DRISK), the Xeomin Review Team, DRISK (review of the proposed Risk Evaluation and Mitigation Strategy [REMS]), Kendra Biddick, Office of Compliance, Dr. Antoine El-Hage, Division of Scientific Investigations, Dr. Barbara Wilcox, pharmacologist, Dr. Lois Freed, pharmacology supervisor, Drs. Ennan Guan, Joao Pedras-Vasconcelos, Jinhai Wang, Susan Kirshner, and Amy Rosenberg, Division of Therapeutic Proteins, Dr. Patricia, Hughes, microbiologist, Dr. Bo Chi, sterility and microbiology, Dr. Mary Farbman, microbiology, and Dr. Dave Podskalny, neurology team leader. The review team recommends that Xeomin be approved. In this memo, I will briefly review the relevant effectiveness and safety data, and offer the division's recommendation for action on this BLA.

Effectiveness

As noted above, the sponsor has submitted the results two adequate and well-controlled studies that purport to establish the effectiveness of Xeomin in patients with either CD or blepharospasm. I will briefly each study.

Blepharospasm

Study 0433/1

This was a parallel group, double blind trial in which patients were to be randomized to a single treatment of either Xeomin or placebo. Patients enrolled in this study had to have received at least two previous treatments for blepharospasm with onobotulinumtoxinA (Botox), the last treatment having been given no less than 10 weeks prior to enrollment in this trial.

The primary outcome was to be assessed at Week 6. Patients were continued in double-blind follow-up for up to 21 weeks, until (or if) they need a second injection. That is, patients were followed for up to 21 weeks to determine the duration of effect of the single study treatment.

In this study, patients were to receive the same dose (total and per each eye) that they had most recently received with Botox, and this was to be delivered in as many locations, injections, and dose/injection as they had received with Botox. Investigators were to mark on a grid (a schematic of both eyes) the number and location of injections they gave. The sponsor presented this data as mean number of injections, mean dose/injection, and location of these injections, this latter divided into the following location categories for each eye (the sponsor did not present data by specific muscle):

Temporal area
Eyebrow area
Upper lid area
Lower lid area
Orbital rim

The primary outcome was the mean change from baseline at Week 6 in the Jankovic Rating Severity Scale (JRS-S), a two item scale that measured Severity and Frequency on a 0 to 4 rating scale. Secondary outcomes included:

1) JRS Severity Subscale Diary, measured by the patient for the 7 days prior to a visit
2) Blepharospasm Disability Index (DSDI), a self-rated scale of 6 items (for example, Driving a Vehicle, Watching TV), on a 0-4 scale
3) Patient Evaluation of Global Response (PEGR), ranging from +4 (complete abolishment of signs and symptoms) to -4 (very marked worsening)
4) Global Assessment of Efficacy, rated by the investigator at the final visit on a 4 point Likert Scale, from "very good", "good", "moderate", and "poor"
5) Time to Onset of Treatment Effect, given in weeks from the treatment to when the patient noted an effect

6) Time to Waning of Treatment Effect, given in weeks from the treatment to when the effect waned. This was only assessed in patients who had reported an effect, and was first assessed at Week 3
7) Duration of Treatment Effect, defined as the number of days between treatment and the agreed upon day of re-treatment

A total of 109 patients (Xeomin 75, placebo 34) were randomized at 31 sites in the US and Canada. A total of 70/75 (93%) of Xeomin patients completed the study, compared to 32/34 (94%) of placebo patients. All patients were included in the primary efficacy analysis.

The following chart displays the results of the analyses of the primary and secondary outcomes.

	Xeomin	Placebo	P-value
JRS-S			
Baseline	3.15	2.94	
Change	-0.84	0.21	<0.001
JRS-Frequency			
Baseline	2.7	2.8	
Change	-0.67	-0.14	<0.014
JRS Diary			
Baseline	2.61	2.53	
Change	-0.9	-0.02	<0.005
BDI			
Baseline	1.60	1.37	
Change	-0.48	0.01	<0.002

PEGR			
Improved	59%	15%	<0.001
Global			
Improved	65%	24%	<0.001

Onset to Treatment Effect

A total of 55/75 (77%) of Xeomin patients reported a beneficial effect, compared to 13/34 (38%) of placebo patients. The mean time to onset of this effect was about 6 days in both groups. A total of 53/55 (96%) of the Xeomin patients reported a waning of the effect, with a mean time to this loss of effect of about 6.5 weeks (range 1-15 weeks). A total of 11/13 (85%) of the placebo patients reported a loss of effect, with a mean time to this loss of about 5.2 weeks (range 0-13 weeks).

As Dr. Bergmann notes, a better way to assess the duration of effect was the time to next treatment, which was agreed to by both the patient and the investigator.

The mean time to the next treatment for the Xeomin patients was 69 days (median 70 days), compared to 54 days (median 43 days) in the placebo group. A total of 40% of the Xeomin patients received their second treatment at Week 6, the time of assessment of the primary outcome, compared to 76% of placebo patients treated at that time point. Although the vast majority of patients in the Xeomin group received a second treatment by Week 10, a few (4.2%) received their second treatment between Week12 and 22.

Dose

The median total dose of Xeomin given was 65 units (range 20-100 units) and the mean was 67 units, distributed equally between both eyes. The mean number of injections per eye was 6 (SD 1.57). The following table displays more details of the dosing.

Total Units injected by area

Area	Mean	Median	Range
Temporal	14	12.5	2.5-30
Eyebrow	8	5	1.3-30
Upper lid	9.4	10	2.5-25
Lower lid	7.3	7.5	2.5-20
Orbital rim	5.6	5	2.5-15

(The numbers are given for the right eye, but are very similar for the left eye).

Number of Injections

Area	Mean
Temporal	2.3
Eyebrow	1.3
Upper lid	1.8
Lower lid	1.5
Orbital rim	1.2

(The numbers are given for the right eye, but are very similar for the left eye).

Open-label, multiple dosing

After the blinded phase, patients were permitted to enroll in an open-label phase, during which they could receive a total of 5 additional treatments, with a minimum of 6 weeks between treatments.

All 102 patients who completed the double-blind phase entered the open-label extension. A total of 89% of patients received either 4 or 5 injections (about half, 56/102, received 5 injections).

There was no important change in the dose of each treatment over the course of the open-label extension (see Dr. Bergmann's Table 29, page 75 of his review). As Dr. Bergmann also notes, there was no material difference in the change in mean JRS over time (see his Table 30, page 76).

For patients who received 5 injections, the mean time between (each) injection was about 77-8 days; for those who received 4 injections, the mean time between injections varied from 94 (between second and third) and 103 (between

third and fourth). For those who received 3 open-label injections, the mean time between the second and third was 122 days.

Study 0003

The sponsor performed a trial in which they compared Xeomin to Botox. This was a formal non-inferiority study, and I will not discuss it in any detail here (Dr. Bergmann has discussed the deficiencies that preclude our relying on this study as a pivotal study). I will only mention one point here.

A total of 148 Xeomin and 155 Botox patients were included in the analysis. As noted by Dr. Bergmann, patients in each group were treated with almost identical mean doses, with essentially identical distribution of doses (not surprisingly because, as with the pivotal study, patients had to have been treated with Botox previously, and the dosing rule was the same as in that previous study).

The mean change from baseline in the JRS was -2.9 for Xeomin and -3.1 for Botox, and the trial met its formal non-inferiority standard. The mean duration of effect was 98 days for both groups with essentially identical distributions.

Cervical Dystonia

Study 408/1

This was a parallel group, double-blind trial in which patients were randomized to receive a single treatment of either Xeomin 120 units, 240 units, or placebo. The number and site of injections was to be determined by the investigator, and patients who had received Botox previously, as well as those who had not, were to be enrolled.

The primary outcome was to be the Change from Baseline in the Total Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) score at Week 4. The TWSTRS is made up of three sub-scales: Severity, Disability, and Pain. Responses in these sub-scales were evaluated as secondary outcomes, as well as Global Assessment of the Investigator, PEGR, Time to Effect, Time to Waning of Effect, and Duration of Effect. Patients were to be followed for up to 20 weeks after the single treatment, until they needed an additional treatment.

A total of 233 patients were randomized (240 Units, 81; 120 units, 78; placebo, 74) at 37 centers in the United States. A total of 94%, 96%, and 92% of the 240, 120, and placebo groups completed the double-blind phase. A total of 90 patients were treatment-naïve (31, 31, and 28 in the 240, 120, and placebo groups, respectively).

The following chart displays the results of the primary, as well as selected secondary outcomes.

TWSTRS Total Score

Dose	Baseline	Change	P-value
240 U	42.1	-10.9	<0.001
120 U	42.6	-9.9	<0.001
Placebo	41.8	-2.2	

TWSTRS Severity Score

Dose	Baseline	Change	P-value
240 U	18.6	-5.5	<0.001
120 U	18.0	-3.9	0.003
Placebo	18.9	-1.9	

TWSTRS Disability Score

Dose	Baseline	Change	P-value
240 U	12.5	-3.0	<0.001
120 U	13.1	-3.3	<0.001
Placebo	11.8	0	

TWSTRS Pain Score

Dose	Baseline	Change	P-value
240 U	11.0	-2.4	<0.001
120 U	11.5	-2.7	<0.001
Placebo	11.1	-0.3	

PEGR	240	120	Placebo
Improved	67%	64%	20%

Global Assessment

Very Good or Good	57%	51%	14%

Previously Treated and Treatment Naïve Patients

There were few systematic differences between the responses of patients previously treated with Botox and those who had not been previously treated (see, for example, Dr. Constantino's Table 24, page 63 of her review).

Time to Onset and Loss of Effect

The mean time to onset of an effect was between 6-7 days in the Xeomin treated patients (SD 7-9 days). The mean Time to Waning of Effect was about 7.5 weeks in the Xeomin-treated patients, and about 4 weeks in the placebo-treated patients (SD about 3.5 weeks).

Duration of Effect

The mean time to a second treatment was about 80 days (range 42-269 days; median 58 days) in both Xeomin groups (SD 22 days) and about 72 days in the placebo patients.

Dose

The following tables (taken from Dr. Constantino's Tables 30 and 31, pages 69-70) describe the range of doses given in each muscle.

Mean (Range) of Dose by Muscle (240 Units)

Muscle	N	Mean Units	Range
Splenius capitis/Semispinalis	79	97.5	40-200
Trapezius	57	62.2	10-200
Sternocleidomastoid	70	52.1	10-120
Levator Scapulae	48	44.4	20-95
Scalene	29	48.1	20-120

Mean (Range) of Dose by Muscle (120 Units)

Splenius capitis/Semispinalis	78	50.5	5-125
Trapezius	55	28.5	5-60
Sternocleidomastoid	63	27.6	7.5-60
Levator Scapulae	49	21.1	7.5-37.5
Scalene	27	21.3	5-50

Other muscles were injected as well. See Dr. Constantino's Table 31, page 70, for a full accounting of muscles and doses injected.

Open-label multiple injection data

After the initial double-blind phase, patients were re-randomized to receive either 240 or 120 units of Xeomin up to a total of 5 treatments (after the initial double-blind treatment) under blinded conditions, no more frequently than every 6 weeks.

Dr. Constantino provided data for 154 patients treated in this open-label phase; the trial was still on-going at the time of her review, with 24 patients still receiving treatment under blinded conditions.

The following table presents the mean and median number of days between injections for each dose (the duration given for the first dose in this table is the number of days since the first dose given in the primary double blind phase of the placebo controlled trial):

Treatment	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
240 units	N=78	N=69	N=69	N=52	N=52
Mean	68	89	88	84	70
Median	58	84	88	87	68
120 units	N=75	N=63	N=57	N=43	N=29
Mean	75	90	100	84	77
Median	57	82	90	84	77

The time from the first (main phase) treatment to the first open-label treatment ranged from 42 days to 269 days. The ranges for the durations between subsequent doses can be found in Dr. Constantino's review, pages 78-80.

The mean total TWSTRS scores at each of these visits varied, but generally were in the range of 35-38 (see Dr. Constantino's Table 34, page 75 for details).

Safety

A total of 1313 patients received at least one dose of Xeomin in all studies combined (431 with CD, 222 with blepharospasm), including indications other than the two under review here (including spasticity).

Blepharospasm

The mean dose in the patients with blepharospasm was 49 units (median 50 units). In the controlled portion, the mean dose was 67 units (median 65).

The following table displays the experience with multiple doses in patients with blepharospasm, taken from Dr. Bergmann's Table 59, page 108 (for each duration [24 and 48 weeks], the patient counts include only those patients who were treated no less frequently than very 12 weeks, and the dose ranges given are for each treatment):

Dose (units)	24 weeks		48 weeks	
	N	Cum N	N	Cum N
100	15	15	13	13
90-99	5	20	4	17
80-89	11	31	5	22
70-79	14	45	12	34
60-69	16	61	14	48
50-59	17	78	18	66
40-49	8	86	8	74
30-39	3	89	3	77
20 or less	3	92	3	80

Deaths

There were no deaths in studies of patients with blepharospasm.

Serious Adverse Events (SAEs)

There were no SAEs in the pivotal controlled trial of blepharospasm in patients treated with Xeomin. In Study 003, there were 2% (N=3) and 3.3% of patients treated with Xeomin and Botox, respectively, who experienced an SAE. The three SAEs in the Xeomin patients were abdominal pain, enterocolitis, and hemorrhagic diverticulum. In the open-label experience, there were 16 SAEs, none occurring in more than one patient (one case each of dyspnea, pancreatitis, convulsion, and bronchitis. Review of these cases suggests that it is unlikely that Xeomin played a role.

Discontinuations

There were no discontinuations for adverse events in the blepharospasm controlled trials. One patient withdrew due to an AE in open-label treatment, due to "post-procedural pain and malignant breast lump removal".

Common Adverse Events

The following table is taken from Dr. Jones's Table 15, page 58 of her review).

Event	Xeomin N=74 %	Placebo N=34 %	Xeomin 10-40 N=13 %	Xeomin >40 N=61 %
Ptosis	19	9	15	20
Dry eye	16	12	23	15
Blurred vision	5	6	0	6.6
Impaired vision	7	0	0	8
Dry mouth	16	3	31	13
Diarrhea	8	0	8	3
Nasopharyngitis	5	3	8	5
Resp Tract infection	5	3	0	6.6
Headache	7	3	8	6.6
Dyspnea	5	3	0	6.6

In the open-label experience, no new AEs emerged. For the most part, the incidence of these events decreased (see Dr. Jones's Table 16, page 118).

Cervical Dystonia

The mean dose in CD studies was 152 units (median 120 units). A total of 67 patients received treatments (of at least 120 units) at least every 12-14 weeks (on average) for between 1 year and 18 months. At total of 24 patients received a dose of at least 120 units every 12-16 weeks for between 6 months and one year. A total of 42 patients received a dose of at least 120 units every 16-19 weeks for between 18 months and 2 years. At least 163 patients received a dose of at least 120 units for at least 6 months, although this does not mean that they received that dose/treatment at least every 12 weeks.

Deaths

There were no deaths in patients treated with Xeomin in trials of patients with CD.

SAEs

In controlled trials of patients with CD, a total of 4 (2.5%) of Xeomin-treated patients experienced an SAE, compared to 0 placebo patients. These patients

all received 240 units; there were one case each of appendicitis, asthma, COPD, and staphylococcal infection. None of these appeared clearly related to treatment with Xeomin.

In open-label CD studies, 11 patients reported 16 SAEs. The following events were reported:

Pancreatitis-2 cases
Cholecystitis
Suicidal ideation
Accidental overdose
Basal cell carcinoma
Colonic polyp
Appendiceal abscess
Respiratory failure
Herpes Zoster
Chest injury
Compression fracture
Lung neoplasm
Intestinal obstruction
Hip fracture

The case of respiratory failure was a 67 year old man with a history of hypertension, hyperlipidemia, hepatitis, and other medical issues who underwent an appendectomy, who returned to surgery 2 days later and found to have blood in the abdomen. He was admitted to the ICU on a ventilator. He had received 2 doses of 240 units each.

The two cases of pancreatitis were not related to Xeomin (one due to blockage due to stones, one due to alcohol).

In other CD studies, 17 patients had at least one SAE; none were reasonably related to treatment with Xeomin (see Dr. Jones's Table, pages 83-5).

Discontinuations

In the controlled study, 2/81 (2.5%), 1/78 (1.3%), and 0/74 (0%) of the 240, 120 unit, and placebo groups, respectively, discontinued due to an adverse event. The two, 240 unit patients had muscular weakness, and the 120 unit patient had dizziness and nausea. In open-label and other studies, 3 more patients discontinued due to an adverse event, none obviously related to Xeomin (pregnancy, malignant neoplasm, MI).

Common Adverse Reactions

The following chart, taken from Dr. Jones's Table 18, page 60, displays the common adverse events seen in the pivotal study.

Event	240 % N=82	120 % N=77	Placebo % N=74
Dysphagia	24	18	3
Neck pain	15	6.5	4
Muscular weakness	11	6.5	1
Nausea	5	3	0
Headache	5	3	4
Musculoskeletal pain	4	6.5	1
Muscle spasm	4	1	3
Muscle stiffness	5	0	1
Dizziness	2.5	2.6	1
Asthenia	2.5	1	0

In the pivotal study and its extension, two patients experienced dyspnea. As described by Dr. Jones (pages 122-3), neither was clearly related to Xeomin, although one that occurred in a 51 year old woman after stair climbing was possibly related (the other occurred in a 19 year old man in the setting of an asthma attack).

In other open-label and other studies, the most common AEs were dysphagia, sinus infection, common cold, and headache and neck weakness.

Spasticity

In a placebo controlled study, 139 patients received treatment for at least 24 weeks, and 127 received treatment for at least 48 weeks (treatments at least every 12 weeks). However, only 31 patients met the Agency's definition of treatment for 48 weeks (that is, received treatments no less frequently than every 12 weeks). In this indication, in the controlled portion of the study and in open-label, 147 patients received at least one dose, 136 received at least 2 doses, at least 121 received 3 doses, at least 100 patients received at least 4 injections, at least 51 received at least 5 injections, and 7 received 6 injections. The mean dose at each injection was between 332-361 units.

Deaths

There were three deaths in patients treated with Xeomin and 2 deaths in placebo patients.

The three deaths in the Xeomin group were a 72 year old man who died in his sleep, who had received a single 375 unit injection 136 days prior to his death; a 67 year old man with a history of hypertension and a CVA who died of cardiac arrest 44 days after a second injection of 400 units; and a 71 year old man with a history of a CVA and hypertension who died 21 days after a second injection of 400 units.

SAEs

In a controlled trial, 4/73 (5.5%) of Xeomin-treated patients, and 1/75 (1.3%) of placebo patients reported an SAE. In the Xeomin-treated patients, there was one case each of bronchitis, cellulitis, status epilepticus and paraparesis, and hypertension and vertigo.

The patient with paraparesis was a 49 year old man who had a hemiparesis at baseline (history of CVA and epilepsy). He developed status epilepticus and paraparesis 31 days after a dose of 170 units of Xeomin.

In the open-label extension of the controlled trial, 26/145 (18%) of patients reported an SAE. As described by Dr. Jones (pages 87-90), none are reasonably related to Xeomin.

In other studies, 17 subjects reported 23 SAEs. Dr. Jones concludes that, again, there is no obvious pattern of events that could reasonably be attributed to Xeomin.

Discontinuations

There were no discontinuations in controlled trials attributed to an adverse event.

In the open-label extension to the controlled trial, 7 Xeomin-treated patients discontinued treatment due to an AE. Reasons included injection site pain, dysphagia, CVA, hypokinesia, and colon cancer.

The patient who discontinued due to dysphagia was a 72 year old man with a history of a CVA, hypertension, hypercholesterolemia, and hemiparesis (ex-smoker). He developed a mild case of dysphagia 9 days after a 310 unit dose of Xeomin, and then again 1 day after his next dose (325 units 3 months later).

In other studies, 3 additional patients withdrew due to an AE; none of them appeared related to Xeomin (CVA, carotid artery stenosis, MI).

Common Adverse Events

The following adverse events were seen in a controlled trial

Event	Xeomin N=73 %	Placebo N=75 %
Headache	3	1
Epilepsy	3	0
Hypercholesterolemia	3	1
Hyperglycemia	4	0

In open-label studies, the following AEs were reported:

Event	%
Spasticity	10
Depression	5
URI	5
Respiratory tract infection	3
Epilepsy	3
UTI	3
Injection site pain	3
Influenza	2
Extremity pain	2
Pyrexia	2
Hyperglycemia	2

Adverse events of interest in patients in spasticity trials

In a controlled study, 1 patient each in the drug (constipation and paraparesis) and placebo (dysphagia) groups had an adverse event that could represent spread of toxin.

In pooled controlled spasticity studies, 6/265 (2.3%) of Xeomin treated compared to 1/75 (1.3%) of placebo patients experienced such an event. In the Xeomin treated patients there were 3 patients with muscular weakness, and one case

each of dysphagia, constipation, dysarthria, and paraparesis (this latter patient is described above).

In open-label extensions, there were 9 patients with events possibly related to toxin spread, including weakness, hemiparesis, dysphagia, and dry mouth.

Laboratory tests

There were no significant shifts from normal to abnormal or changes in means for any laboratory parameters in any of the (b) (4) indications studied. In general, labs were assessed at baseline and at the final visit (which was often weeks after the final treatment), or at the time of the primary effectiveness assessment (also weeks after the treatment).

Because analyses of previously approved botulinum toxin type A products (e.g., Dysport) suggested a slight mean increase in serum glucose and alkaline phosphatase, Dr. Jones examined the pooled data for changes in these parameters (pooled data included, obviously, more patients than studied in the individual indications, and might have provided a more sensitive test of whether or not Xeomin is associated with small changes).

In these analyses, there were also no consistent changes in mean values between drug and placebo-treated patients.

As Dr. Jones notes, however, there were 5 patients across the (b) (4) indications who were noted to have elevated glucose levels of interest:

1) a 48 year old man with blepharospasm who received a total of 6 doses (one in the controlled trials, one in open-label. The patient had the following glucose levels before the 3rd, 5th, and 6th injections, respectively: 140 mg/dL, 160 mg/dL, and 198 mg/dL.
2) A 68 year old woman who received two doses of Xeomin, one in the controlled phase, one in open-label. Before the 2nd treatment and before the last visit, her serum glucose was 173 mg/dL and 126 mg/dL (the latter was the same as at screening), respectively.
3) A patient in a CD study had a glucose of 7.5 mmol/L (ULN 6.1) before the 4th treatment (last 3 treatments were 240 units).
4) A patient in a CD study had a glucose of 2.9 mmol/L (LLN 3.8) at the last visit.
5) A woman with a history of diabetes was noted to have a glucose of 432 mg/dL at Visit 8, and was hospitalized for control of her diabetes. Subsequent levels were either high, low, or normal.

Regarding alkaline phosphatase levels, again, in the pooled analyses, there were no important changes. However, there were 3 patients who had elevated levels of interest.

1) a 72 year old woman had an abnormal Alk phos at the final visit: 134 U/L (ULN 118 U/L). She had received a single dose of 240 Units in the controlled portion, and 3 treatments (still blinded: either 240 or 120 units) in open-label.
2) A patient in a spasticity study had an alk phos of 172 U/L before the 4th treatment.
3) A 56 year old woman in a glabellar lines study received 4 treatment cycles and at the 12 month evaluation was noted to have had an alk phos of 171. Of note, during the study she was noted to have a bile duct stone for which she was hospitalized, and "moderate" gastritis.

Vital signs

Blood pressure was measured at baseline, and before subsequent injections in the extension periods for the blepharospasm, CD, and spasticity controlled trials. There were no meaningful effects on pulse or blood pressure. However, it should be again noted that, for the most part, these were assessed at treatment visits, but prior to any injections being given at that visit; that is, weeks after the previous treatment was given.

EKG

Although EKGs were not systematically performed post-baseline (usually only done in the setting of a potential cardiovascular AE), there were no obvious clinically significant changes in any EKG parameter.

Immunogenicity

(b) (4)

According to the sponsor, 12/1080 (1.1%) of subjects who were antibody negative at baseline developed neutralizing antibodies during the course of their participation in studies. Of these 12, 9 patients were still positive for antibodies at the end of the study.

In comparative studies with Botox, 0.7% developed antibodies, compared to 0.8% in the Botox patients.

In blepharospasm studies, 4 patients who were antibody negative at baseline developed "borderline" positive values during the studies. No patients in the open-label period of the pivotal study developed antibodies. Two of these

patients developed AEs (one mild malaise, one ear infection, nasopharyngitis, worsening hypertension).

In the CD controlled trial, in the primary phase, 4 patients developed a positive antibody test. One patient experienced an AE (bilateral leg and arm pain and weakness).

In addition, 4 other patients developed antibodies during open-label treatment. In at least one of these patients, a subsequent test was negative for antibodies.

In a controlled study with an open-label extension, no patients became antibody positive (antibodies measured before each injection, 4 weeks after the second injection, and at the end of the study). As noted by Dr. Jones, the following number of patients received the corresponding number of injections:

	Number who received the:
First injection	47
Second injection	136
Third injection	121
Fourth injection	100
Fifth injection	51
Sixth injection	7

Non-clinical

Although the pharmacology team finds that the studies performed by the sponsor were adequate, they recommend that the sponsor perform a pre-and post-natal development study, as well as a juvenile animal study (the latter to support clinical studies in pediatric patients to be described below).

Product issues

The product team recommends that the application be approved, but they have proposed numerous post-marketing commitments.

Comments

The sponsor has submitted one adequate and well controlled trial in patients with blepharospasm and one adequate and well controlled trial in patients with CD. The review team finds that these studies establish substantial evidence of effectiveness for Xeomin for both of these indications, and I agree without reservation.

One issue that requires some discussion is the matter of the appropriate dose for each indication.

For blepharospasm, the controlled trial enrolled patients who had been treated previously with Botox, and in the trial they were to receive (and did receive) the same dose of Xeomin that they had received previously with Botox. Clearly, this generated an effective dosing strategy, though there is no evidence that patients experienced a similar degree of effectiveness (or tolerability) with Xeomin as they did with Botox. Nonetheless, I believe it is reasonable to recommend that patients initially be treated with the dose they previously received with Botox. If that dose is not known, I believe the data permit us to provide guidelines for an appropriate starting dose (based, admittedly, in part on the labeling for initiating treatment with Botox).

There were no specific, standardized dosing instructions in this study regarding placement of injections, dose/injection, or actual dose (though there were limits placed on total dose). Investigators were simply instructed to replicate the previous treatment with Botox in all the particulars. The data with regard to location of injections was simplified by the sponsor, by which they aggregated the various (and numerous) locations that investigators used into 5 separate locations (not by individual muscle), and presented the data (dose/ injection) by region, as well as by number of injections. This approach has made it somewhat difficult to provide dosing recommendations, but I believe that the data can be distilled into reasonable guidelines for total dose, site for injections, dose/anatomical site, and total number of injections/treatment.

Regarding long-term treatment, the controlled trial was only a single dose study. However, the sponsor has presented data on the time to nth injection, and on the response to specific doses over time. Although these data are open-label and uncontrolled, they are consistent with the sort of long-term data obtained for other products approved for the treatment of blepharospasm (i.e., Botox), and, in my view, provide reasonable data to support statements in product labeling about dosing over the long-term.

In many meetings with the sponsor prior to the submission of the BLA, the division made it clear that the sponsor should include patients who had not previously received treatment with Botox. Although the sponsor had argued that it would be difficult to enroll many such patients, we were under the impression that they would do so. They did not. I believe there is an argument to be made that, despite this, Xeomin should be approved for treatment-naïve patients. One could argue that the current study establishes that Xeomin is an effective treatment for patients with blepharospasm; the fact that the patients enrolled in the trial had previously responded to Botox is, in effect, really only an enrichment procedure, and that there is no reason to believe that previously untreated patients would not respond (of course, we would not know which such patients would actually respond, but, as a general matter, we don't know that for most, if not all, treatments for most any indication). However, the matter of the starting dose in treatment-naïve patients has not been addressed in this application; in

addition, the sponsor has made no argument in the submission to convince us that treatment-naïve patients should be included without some empirical data in this subset. I am, therefore, comfortable with recommending approving the application for previously treated patients, at this time. The sponsor may, of course, subsequent to approval submit a supplement to obtain an indication in the treatment-naïve population.

Finally, the sponsor proposes that the product be indicated for patients with benign essential blepharospasm. As Dr. Bergmann points out, this is a somewhat antiquated term, and, more importantly, a sizeable subset of the patients in this study had blepharospasm in the context of other dystonias. Therefore, we recommend that the product be indicated simply in patients with blepharospasm.

Regarding CD, the sponsor has performed a fixed dose study. In this study, there is little evidence that a dose of 240 units is materially more effective than a dose of 120 units, and we would recommend that this latter dose be the recommended dose.

Although the doses were fixed in this study (unlike in the blepharospasm study), like in the blepharospasm study, the sponsor gave the investigators little specific guidance about number of injections or location of injections. Nonetheless, we believe that the data have been presented in such a way that reasonable guidance on these points can be given in labeling. Unlike the case with blepharospasm, the sponsor did enroll treatment-naïve patients in this study, so there is no reason to restrict the claim to patients who have been previously treated.

Like the blepharospasm case, the controlled trial was only a single treatment trial, but the open-label, uncontrolled extension has provided meaningful data (in terms of dose and frequency of dosing) on which to base dosing recommendations for the long-term. In particular, there seems to be no significant change in patient response or specific total dose requirements over time (for at least as long as the study was).

Regarding safety, Xeomin appears to be associated with adverse reactions well known to be caused by these products, and there do not seem to be any novel AEs seen in this development program. Regarding the particular concern about distant spread of the effects of the toxin, there were cases in which spread appears to have occurred, although there were no cases of a life-threatening event attributable to this mechanism. Nonetheless, the label should include all of the labeling statements warning about this risk that appear in other related products.

All review teams recommend that the application be approved, but several groups have recommended that the sponsor complete post-marketing studies.

The clinical group proposes post-marketing requirements (PMRs) for:

1) a 12 month safety study in pediatric patients with upper and lower limb spasticity, and
2) a similar study in adults

These studies have been required for all other botulinum toxin products.

In addition, the clinical group recommends the following post-marketing commitments (PMCs):

1) a controlled trial in pediatric patients with upper limb spasticity
2) a controlled trial in pediatric patients with lower limb spasticity
3) a controlled trial in adults with lower limb spasticity
4) a controlled trial in adults with upper limb spasticity
5) a controlled trial in botulinum toxin-naïve patients with blepharospasm

The first four of these have been required of all botulinum toxin product that do not already have such a claim.

The pharmacology group recommends 2 PMRs: a pre- and post-natal development study and a juvenile animal toxicity study (the latter is necessary before clinical studies in pediatric patients can be performed).

The Division of Therapeutic Proteins has recommended numerous PMCs (see the Approval letter for the specific PMCs).

Finally, the sponsor has proposed a Risk Evaluation and Mitigation Strategy (REMS) that consists of a Medication Guide and a Communication Plan (the latter consists of a Dear Health Care Provider letter). The proposed REMS has been reviewed, and found to be acceptable.

For the reasons described above, we recommend that the BLA for Xeomin for the treatment of patients with CD and for patients with blepharospasm who have been previously treated with Botox should be approved, with the agreed upon product labeling and Medication Guide.

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