Public Comments Received on "*Controversies in Migraine Management*"

1. Benjamin Frishberg, MD, Neurologist, The Neurology Center of Southern California, Encinitas, CA
2. Alan M. Rapoport, MD, President, The International Headache Society; Clinical Professor of Neurology, The David Geffen School of Medicine at UCLA, Los Angeles, California
3. Jack Schim, MD, Neurologist, The Neurology Center of Southern California; Encinitas, CA
4. Lawrence Newman, MD, FAAN, President, The American Headache Society; Director, The Headache Institute, Mount Sinai Roosevelt Hospital Center, New York, NY
5. American College of Emergency Physicians
6. James Youngdale
7. Ramona Monroe
8. Seymour Diamond, MD, Executive Chairman and Founder, National Headache Foundation, Chicago, IL
9. Joy Howard, RN, BSN, Owner/Educator, Dental Ed, Inc., Carlsbad, CA
10. Valerie Kenna
11. Karen Bale, Vista, CA
12. Michael Glen
13. Tammy
14. Brian Kennedy, Executive Director, Alliance for Patient Access, Washington, DC
15. Karen Campbell, PharmD, Senior Medical Scientific Manager, Medical Affairs, and Jonathan Kowalski, PharmD, MS, Vice President, US Health Outcomes, Allergan Inc., Irvine, CA (2 sets of comments, one from 7/2/14 and one from 7/22/14)

THE NEUROLOGY CENTER

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Brian Belnap, D.O.
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Irene Oh, M.D.
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Jay H. Rosenberg, M.D
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Medical Neurology
Medical-Legal Evaluations
Neuro-Diagnostic Testing

Neuro-Ophthalmology
Neurologic Rehabilitation
Sleep Medicine

Botox Therapy
Headache Medicine
Epilepsy Monitoring

To whom it may concern,

I am a neurologist in private practice in San Diego. I am a specialist in headache and board certified in Headache Medicine. I have been using Botox for treatment of facial spasms since 1985 prior to approval in 1989, and have been involved in early phase II clinical trials with Botox beginning in 1998. I am one of the named authors in the large phase II study that led to the PREEMPT studies in which I was a principal investigator. I was on the US Headache consortium which released the first Evidence Based Guidelines on the use of Preventive Treatment of Migraine in 2000.

While the clinical trials did not show a remarkable difference in reduction in headache days, as compared with placebo, my experience in the real world is a very different picture. The current requirements in order to obtain coverage by commercial insurers requires patients must have tried and failed 2 or 3 preventive agents in 2 or 3 different classes. Therefore, all of the patients I treat with Botox for chronic migraine have typically failed beta-blockers, topiramate, and a tricyclic antidepressant such as amitriptyline.

For the most part, anecdotal reports have little meaning as compared with randomized, double blinded, placebo controlled studies or a meta-analysis; however for those of us in the trenches taking care of patients daily, the patient experience speaks louder than any clinical study. I will state that I have dozens of patients with chronic migraine who have failed multiple oral therapies who have 50-90% reduction in headache days after a cycle of injections. When I train residents in my clinic, they all leave with a highly positive impression of the efficacy of Botox after they meet patient after patient who report “life changing” improvement in their headache disability.

It is always difficult to create models that accurately reflect the reality of patient care. I take exception with many of the statements, which are a result of a careful “analysis” of the literature. Comparing the efficacy and tolerability of Botox and Amitriptyline is like comparing apples and oranges. The approval of amitriptyline by the FDA is based on a study of Dr. James Couch of 72 patients in 1972. The tolerability of amitriptyline is limited by sedation and weight gain as well as dry month. AS well, studies of medication for treatment of chronic migraine are limited and small in scale.

I also disagree with your economic modeling by stating costs that are not real world. You report the cost of a year of metoprolol as $42 while the cost of Botox is $8,000/year. This suggests a bias on the part of the folks compiling this data. My patients seem to pay at least $10 and usually $20 for a month supply for any generic drug if they are using insurance. Also, the cost of a vial of Botox is about $560. We use 2 vials for Botox at a cost of $1120 and injection cost of $150. Adding a 10% profit for the drug (CMS give 6%), this comes to $1300/injection with 4/year which is closer to $5200. While this is on the low end, 8K is a large overestimate and suggests bias on your end.

While we all have an interest in reducing the skyrocketing costs of health care, and we want to use our limited resources wisely, one must be careful about limiting what has come to be, what I believe to be the most effective treatment for chronic migraine with tolerability and safety that are remarkable, especially when provided by an experienced injector.

I would ask that you be very careful in making or advising a large change in policy that may lead to unintended consequences or limits the availability of Botox therapy to those who have found it highly effective after failing standard therapies.

Disclaimer: While I was a speaker and consultant for Allergan in the past, I no longer receive any compensation or monies that relate to Botox except for may care of patients.

Benjamin Frishberg MD
6/30/14

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6-30-14

To whom it may concern,

I have seen the agenda, the draft assessment and a document outlining the CTAF assessment scope and voting questions related to this assessment about Botox. I believe that you should postpone this meeting and have the questions you pose properly evaluated in light of the more recent studies done of Botox.

It is inappropriate to compare 2 drugs which are not approved for a condition, evaluated in a trial done outside the US, when neither of the drugs is the one you are making a decision about. It is even more inappropriate for a group of companies that exist to save and make money, to make a health care decision about a drug that is approved for a certain condition, that those companies do not want to have to cover.

If you are serious about an evaluation, have it done by neutral medical specialists, evaluating appropriate data, according to the highest medical principles. I suspect what you are suggesting borders on restraint of trade. I believe it could make reasonable patients and physicians very upset and could possibly backfire for your organization.

I am writing this as a private physician in California. I care about fairness in medicine and you have conducted an unfair comparison which I reject out of hand.

Alan Rapoport

Alan M. Rapoport, M.D.

Clinical Professor of Neurology
The David Geffen School of Medicine at UCLA in Los Angeles, California

President
The International Headache Society (IHS)

Email: alanrapoport@gmail.com

7/1/14

I am a neurologist in a large group, and co - director of a headache center in San Diego. The majority of my practice is headache focused, and thus I find it crucial to make some comments on the controversies in migraine draft review.

I have been an investigator in many headache studies, including many of the Botox vs placebo studies as well as pilot studies of Botox vs divalproex and vs topiramate. While all 3 topics in the review are important, I will focus on the use of onabotulinumtoxinA (Botox) for migraine treatment.

The premise that cost of a day of migraine is a fixed number neglects the variety of occupations and thus cost of a missed day to individuals. As an example, I have a patient who is a police officer, and was on the verge of losing her job due to migraine induced absenteeism. She has had Botox treatment for about 5 years, and has had such reduction of headache days and migraine related disability that she has been promoted to sergeant, and has had no missed days of work for a couple of years. While anecdotes are not solid science on their own, there are numerous studies on migraine personal, disability, and economic impact. Without input from individuals with migraine, to understand the impact of chronic migraine, any analysis of the impact of treatment is likely to misunderstand the importance of a new therapy.

There are a number of methodologic issues that need to be addressed before this report could reasonably be voted upon. It is recognized in scientific literature that meta-analysis is based on the premise that studies that are aggregated enrolled similar populations, and had comparable treatment arms, so that the statistics are meaningful. The analyses of Botox for migraine should thus be restricted to those that studied its use for chronic migraine, as studies of episodic migraine have defined that as a non-responsive population to the specific injection regimen. On a speculative basis, perhaps the PREEMPT injection protocol might show benefit for the treatment of high frequency episodic migraine. However, coverage and regulatory approval is limited to chronic migraine, so analysis should be similarly shaped. The systematic reviews cited lumped the major studies which were adequately powered to discern treatment effect from placebo, with studies done with differing methodologies and study populations.

The article by Magalhaes (Clin Neurol Neurosurg. 2010 Jul;112(6):463-6.) on Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine, which was used as the basis of the value analysis is very problematic. It did not even look at Botox, but a different Bot-A product, Dysport. The package label for all botulinum products notes that the drugs are not interchangeable, and that there are no relevant dosing ratios. A recent review concluded "Currently, there are three commercially available BTX-A preparations available: Botox, Dysport and Xeomin. They have similar mechanisms of action but their chemical formulation, clinical potency, migration and diffusion as well as safety profile seem to be different. This may result in problems of bioequivalence, not only clinical but also economic ones. .... Each BTX-A formulation should be treated as a different medication and used cautiously according to the individual range of dosages established in clinical trials." There are no meaningful studies of Dysport for chronic migraine.

There are no quality studies of amitriptyline for chronic migraine, with the only recent citation (Couch, Headache. 2011 Jan;51(1):33-51) dating to a study done between 1976 and 1979, without current methodology or headache definitions. Comparing an unproven treatment with another unproven treatment is pointless.

There are multiple other issues that need be addressed before the report can be considered ready for vote. I suggest the public comment period be held open for at least another month, so other stakeholders, such as people with migraine, can give input as well.

Jack Schim, MD

7/2/14

Dear Members of CTAF:

I am writing in my capacity as President of the American Headache Society. Since this is an issue that will have a profound impact on the lives of the patients in whom we have been entrusted, we strongly believe more time is needed to fully review the data. As Headache Medicine Providers, we believe that:

1. There is clear evidence to demonstrate that the net benefit of onabotulinum A injections every 12 weeks are superior to no treatment for chronic migraine, and
2. There is inadequate evidence to demonstrate the comparable effectiveness of amitriptyline to the net benefit of onabotulinum A for the preventive treatment of chronic migraine. There are no placebo-controlled studies that have evaluated the efficacy of amitriptyline for the preventive treatment of chronic migraine. Fur thermore, the small comparator study cited was underpowered, uncontrolled, and did not evaluate Botox, since a differ ent formulation of botulinum toxin was used.

As this decision will affect the lives of many chronic migraine sufferers, it must be made only after carefully reviewing all relevant data. At the present time we do not believe that this report, in its current form, accurately represents the published clinical and cost-effectiveness data with respect to the use of onabotulinum A in the treatment of chronic migraine.

Sincerely,

Lawrence C. Newman, MD, FAAN
President, The American Headache Society

Director, The Headache Institute
Mount Sinai Roosevelt Hospital Center
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NY, NY 10019

7/2/2014 from American College of Emergency Physicians (ACEP)
Thank you for the opportunity to review your draft report: Controversies in Migraine Management. We referred your report to two expert reviewers with the responses below.
Of note, we will be commenting only on the use of opioids in the emergency department in patients suffering a migraine headache; we will not be commenting on the use transcranial magnetic stimulation, transcutaneous electrical nerve stimulation, or Botulinum toxin A (Botox) injections for the prevention of chronic migraines since these are outside of the scope of practice of emergency medicine.

Reviewer #1:
There is not much data on opioids. It can be said that meperidine is modestly but not substantially less efficacious than DHE combinations and the anti-emetics for acute headache. There is no high quality data on hydromorphone, the opioid currently used in 25% of all ED visits. These days, meperidine is used in just 7% of ED visits. It is not known for certain whether meperidine is associated with more recidivism and more headache recurrence than non-opioid comparators (published data that make this claim do not control for severity of underlying migraine disorder). Data on ED LOS is conflicting. Data on adverse events is conflicting and depends on which adverse event one is most interested in (i.e. dizziness vs akathisia).
The authors build their cost-saving analysis on the costs associated with transformation of episodic migraine to chronic migraine and on opioid dependence. There is no evidence that receiving hydromorphone intermittently in the ED is associated with either.
I agree with this statement: "The field would benefit from large, high-quality randomized trials comparing the efficacy and adverse effects of the commonly used therapies for severe migraine headaches in the ED".

Reviewer #2:
This is an interesting document using evidence to create economic models estimating costs/savings of two newly approved devices for the management of migraine headaches, as well as two more established drug therapies. For prevention of migraines, they reviewed the evidence for a transcutaneous electrical nerve stimulation (TENS) device called Cefaly and the evidence for botulinum toxin A (Botox) injections. For the treatment of migraine headaches with aura, they reviewed studies on transcranial magnetic stimulation (TMS) and a newly approved device called SpringTMS.

Of interest to emergency physicians, they also reviewed treatment of migraines in patients in the emergency department setting who have failed self-management and home medications. They reviewed evidence of comparative effectiveness as well as short- and longer-term harms, focusing specifically on the role of opioids. As an evidence-based document, published studies guide the analyses and recommendations. Their model relies heavily on the theory of costs of transformation from episodic to chronic migraines and costs of opioid dependence (p46). While the model uses existing data to calculate costs, the accuracy of the data that the model is based on is open to debate.
p 49 “Certainly, the use of parenteral opioids in the ED, which are employed in over half of all ED visits.” While this may be estimated from published data, this has never reflected practice patterns in the institutions where I have been practiced. Anecdotally, several of our opioid-dependent patients are referred to the ED by neurologists specializing in headache treatment for opioid administration. I suspect that current opioid administration in ED for migraines is far less than one-half of the encounters.
The unstated assumption is that emergency departments are the major source of opioid access for patient. Not administering opioids in the ED would not prevent patients from receiving opioids in other settings, and “transformation” might still occur, meaning that estimated cost-savings are inaccurate. Additionally, to place the burden of opioid dependence on ED administration of opioids is simply unrealistic and the cost savings estimated are thus suspect.
They make no recommendations. The overall gist is that opioids should be infrequently administered in the ED for treatment of migraines. I am in agreement with this, but the arguments in the document while interesting are not compelling.

7/2/14
My name is James Youngdale. I am a 72 year old male. I have had a life long problem with migraine headaches. (My Mother suffered from them). I have tried most of the drug treatments through out my life with little effect accept for two. (Imitrex and Botox)
I have been made aware of your up coming assessment report on the treatment of migraines and would
like to give some input.

My migraines started in my early twenties with one to two migraines a year to five to ten a year by my mid fifties. Most were severe.
Up to that point I used over the counter drugs (mostly aspirin) for relief, but none really helped.

I finally went to the doctor who put me on sumatriptan which I used when I got a migraine, it helped a lot. (we tried several drugs but Imitrex seemed to work best)
At that time I also was beginning to have pain in my lower back (I say this now because it leads to how
I became involved with Botox). This mode of treatment (Imitrex) continued until I was 70 years old.
However in early 2011, (I was 68 years old) I finally had surgery on my back. The surgery went well but after that my migraines got a lot worse. Through out 2011 and 2012 my migraines were so frequent
and severe that I spent most of my time in bed. I started going to a migraine specialist to see if I could get any help. He tried several different drugs but none helped as much as Imitrex. At this point I was down with migraines more that 15 days a month. My specialist suggested that I try Botox. I was an engineer and scientist all my working life and all I ever heard about Botox was that it was used to erase wrinkles. I was very skeptical. But I thought about it, I had tried almost everything else, so why not Botox. So I got my first treatment and had to wait 12 weeks for the second. I really didn't notice any change between the first and second treatment (I wasn't surprised). After the second treatment, about 4 weeks before my third treatment, I was starting to notice that my migraines were coming a little bit farther apart and were not quite as severe as they usually were. This improvement seemed to get better with time. Between my third and forth treatment my migraines got even less frequent and less
severe and I was noticing a positive change in my daily activities. Between my forth and fifth treatment I only had two migraines. I have just had my sixth treatment and I haven't had a migraine for 13 weeks.
After more than a year on Botox I have experienced a level of improvement that I never thought I would. Now I'm a believer.
I hope this will be usefull.

7/3/14

I have been getting migrains since i was a little girl ive been on all kinds of pills ,nothing has worked. My migrains have caused me to leave work miss family gatherings and just stopped a good part of my life if youve ever had a migrain you would know what im talking about.The pain is very bad.I use to get headaches 3 to 4 days a week ,couldnt eat and keep food down .i cant say enough about Botox it has saved my life.Ive been to ER a few times its scared the heck out of me.Since ive been getting botox ive been able to live a normal life.Alot of things cause migrains so without botox id be a mess.ITS THE ONLY THING THAT HAS HELPED.I would like to keep getting botox. I really dont like getting the shots however its way better than getting a migrain.Iget them super bad to where you just cant do anything,the pain is so bad you just want to cut your head off it scares me.I hope you will really think about this so many people suffer with migrains you would be hurting alot of people if you stop botox.Thank you for takeing time to read this i could go on forever about this and how it helps me to live a normal life but im sure you understand how important botox is to me.IVE HAD NO SIDE AFFECTS takeing botox just NO MORE MIGRAINS.

Thank you Ramona Monroe

7/3/14
To the CTAF Advisory Board:

In my position as Executive Chairman and Founder of the National Headache Foundation, I have had the opportunity to review the Draft Report on *Controversies in Migraine Management – A Technology Assessment*. This report was drafted by the Institute for Clinical and Economic Review. I considered the questions to be discussed at the public meeting on July 11, 2014, in view of my 50+ years of practicing headache medicine.

My responses to the questions put forward are:

1. No, there is not sufficient evidence to demonstrate the efficacy of transcranial magnetic stimulation (Spring TMS).

2. No, there is not sufficient evidence to demonstrate the efficacy of the device – Cefaly.

3. Yes, there is more than sufficient evidence to demonstrate the benefits of Botox injections in the prevention of chronic migraine.

   3a. The comparative value of Botox injections versus no treatment in the prevention of chronic migraine is high.

4. This question is difficult to reply with a yes or no answer. I would suggest that it be rewritten in order to provide an adequate response.

5. No. Evidence is not available to demonstrate that the net health benefits of parenteral opioids are inferior to the non-opioid alternatives.

If you have any questions, please contact me at 312-274-2653 or sdiamond@headaches.org.

Sincerely,
Seymour Diamond, MD
Executive Chairman and Founder
National Headache Foundation
820 North Orleans, Suite 411
Chicago, IL 60610

To Whom it may concern,

As a sufferer of chronic migraines I would like to tell you about the benefit I've received from the use of Botox over the last several years. I have suffered from migraines for over 10 years following neck surgery and have tried every available treatment with varied success. Before I went to my neurologist, Dr. Schim, I was getting migraines almost daily. Not only did I have severe headaches, but I also had sensitivity to light, sound and nausea. I found Topamax helpful but experienced unacceptable side effects including a kidney stone. I've also had very good success with Imitrex, and similar products, but these are only helpful for short term treatment since they can exacerbate the migraines if over used and they don't prevent further reoccurrence. On several occasions they have become so bad that I've had to have cortisone injections into my neck and head. As painful as these are, the migraines are worse.

I own my own business and for the last 26 years have been teaching in dental offices. My clients schedule me a year in advance so they can get their annual OSHA training updates. When I am unable to teach, due3 to a migraine, it is a major inconvenience for them as well. I lose $750 for the day in revenue and the doctor has scheduled the day for training so he has no patients scheduled. He has all of his staff there with nothing to do and he has to reschedule with me another time that is convenient for us both. They will not tolerate this more than once before they no longer use my services.

A few years ago Dr. Schim suggested I try Botox. I didn't notice much change after the first injections but by the second injections I was having fewer migraine days. After the third injections my quality of life was greatly improved. Instead of wondering when the next one would hit I was able to plan my personal and professional life again. I was also noticing fewer related symptoms.

There came a time, however, after about the first year of treatment when I could no longer afford the Botox and my migraines returned as before. Again, I tried a variety of treatments, including acupuncture and various medications with little success. Once Botox was approved by insurance I was again able to receive the injections. Now I get them every three months and I am so grateful for my improved quality of life. I rarely need to take Imitrex now and have many fewer "down" days. About a week before I am due for treatment I will start waking up at around 4 in the morning with severe migraines and related symptoms. Once I again have Botox the migraines subside after about a week and this lasts for another 3 months.

I understand that Botox is expensive for the insurance companies but it is an important resource for those of us who are proactive about our medical care and want a healthy, active lifestyle.

Thank you for your consideration,

Joy Howard, R.N., B.S.N.
Owner/Educator
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joyhoward@dentaledinc.com

To Whom It May Concern:

I wanted to write to you from a patients perspective about your report on Controversies in Migraine Management. I found your conclusions on Botox particularly troubling.

I have suffered from headaches/migraines since the onset of my menstrual cycle when I turned 12 years old. I have been through the gamut of preventative medications as well as rescue medications. On average, without medication, I have 20 or more headache days per month. Of those headache days, 5 would usually be severe migraine days that would keep me from regular activity or would reduce regular activity.

Topamax did have good result for me, but I suffered from major side effects including kidney stones large enough to have to have surgically removed.

I am now being treated every 10-12 weeks with Botox. My headache days have been reduced to 3-4 per month on average, usually around my menstrual cycle. I haven't had a severe migraine in at least 9 months.

I used to miss major events in my life & my family's life. Botox has made a significant difference in my daily life. I find it absurd that you valued a missed day at $41 dollars. That doesn't even cover my missed day of work let alone any event in my life that you cannot possibly put a value on!

Patients like me need this treatment.
Sincerely,
Valerie Kenna

To Whom It May Concern,

I have been suffering from migraine headaches for 13 years. They have gotten worse every year of my life to the point where I was afraid to plan ahead for anything. It seemed that anything and everything could trigger a headache. I clench my teeth and that causes my jaws to become sore and my gums to inflame, even with mouth guards. I have tried so many medications it's ridiculous, and unfortunately, none of them worked. When the pain is excruciating a shot of Toradol can bring the pain down to a manageable level.

I started Botox injections over a year ago. I didn't want to; I didn't want a foreign substance injected into my head. I saw no difference the first three times and I was ready to stop, but my doctor suggested I stay with them awhile as the clenching in my jaw was so strong. Finally, after the fourth treatment, I noticed that I didn't clench as hard and there were even nights when I could sleep without my guard. Over the course of 14 months I have gone from 20-plus headaches a month to 5-10. I don't believe this is a coincidence as I have tried so many other medications that did nothing to help. I notice that my jaws aren't as sore in the morning, and I am so pleased that my gums aren't inflamed and painful every morning from clenching so hard.

My quality of life has returned as a result of fewer headaches. I can take trips, be active, be with my family and friends, and not worry if I'm going to be hit with a headache that essentially cannot be treated. When I do get a headache now, I notice I am more relaxed because I know I won't have another one the next day and the day after. I know the headache will probably last a few hours and go away with Imitrex and/or Tylenol and Codeine, something that didn't happen before. The pain in my right temple and jaw were always there and always painful and no medication helped with the pain. Now, the pain is minimal and sometimes, not there at all.

Six months ago I would have told you that Botox didn't do anything for my headaches. Now, I look at my pain journal, and I am shocked at the difference in the amount of headaches I used to have compared to the amount I have now. I really believe that the injections of Botox have relaxed my jaws and the nerves in my face and head so that I am not in constant pain and sometimes, agony. It is a wonderful feeling to know that I can go to sleep and I won't be greeted with blinding pain when I wake up. For me, these injections have changed my life.

Sincerely,

Karen Bale
1219 Via Del Cerro
Vista, CA 92084
(760) 470-1629

Botox is been a life changer for me. There is no value that you can put on it would be too high.

Michael Glen
Dave Stubbs Real Estate
858.414.2373
michael.glen@davestubbs.com
www.SignatureHomesSanDiego.com

My name is Tammy and I fully believe in the Botox treatment for migraines. I was having a terrible time over 2 years ago with migraines and since being on the Botox treatment plan have been migraine free for over 1 1/2 years. I do a combination of Topamax for prevention and the Botox every 12 weeks and will continue to do so. I have my life back and can't be happier! I hope this helps.

July 3, 2014

California Technology Assessment Forum
c/o Institute for Clinical and Economic Review
One State Street, Suite 1050
Boston, MA 02109

Delivered via email: ctaf@icer-review.org

Re: Controversies in Migraine Management (Draft Report of June 13, 2014)

Members of CTAF Advisory Board,

I am writing on behalf of the Alliance for Patient Access, a national network of physicians who advocate on behalf of patient access to approved therapies and appropriate clinical care. I recently had the opportunity to review the above referenced Draft Report and from the perspective of a headache patient advocate I found troubling the methodology and conclusions. Relying on meta-analyses and economic outcome models, the authors fail to take into account the value of the subject therapies and interventions to the individual patient whose symptoms have been improved or completely alleviated by one of these treatments deemed "controversial." This is the inherent danger of coupling comparative effectiveness and cost effectiveness, and inevitably risks undermining patient access to appropriate care.

There is no controversy that headache is prevalent, costly, and for far too long neglected by researchers, governments, and the bio/pharmaceutical and medical device industries. Nearly twenty-percent of the population will suffer from some form of migraine this year, and 3/4 of them will be women. Chronic migraine is much less prevalent but can be absolutely debilitating to those who have to contend with this condition – experiencing over 15 days of symptoms per month. The relatively recent approval by FDA of some of the treatments reviewed in the above referenced Draft Report, represent the only new hope in a generation for millions of migraine suffers.

What is controversial is when studies conducted under the guise of comparative effectiveness or evidence based research invoke cost effectiveness as a means to restrict patient access to only the least costly alternative. Clinical decisions must be based upon what is best for each patient, rather than the economic incentives promoted by the benefit design. A single, centralized cost-effectiveness determination does not reflect the real-world needs of providers, health plan decision-makers, and patients with differing co-morbidities contending with a disabling condition.

AfPA asserts that evidence based research and comparative effectiveness studies should be designed in a manner such that physicians could utilize the findings to further patient care with appropriate options to apply approved therapies. For the findings of comparative effectiveness research to benefit patient care, protocols must be employed to ensure that the unique needs of each patient are recognized. Comparative effectiveness studies typically focus on large populations and do not take into account the impact of gender, race, socioeconomic status and medical co-morbidities of individual patients. Most importantly, individual patients often respond very differently to the same treatment depending on all these factors in addition to other medications they are taking and family history. Therefore, health policies derived from studies that treat all patients in the same manner mean that many patients will not have access to appropriate and FDA approved therapies.

Given the economic costs and denigration of quality of life experienced by migraine patients, it is bad policy to limit the choice of approved therapies a patient's physician might consider when determining the best course of treatment. Accordingly, the AfPA urges the members of the Board to reject the Draft Report, reaffirm the primacy of the physician-patient relationship in the provision of quality care, and recognize that patients benefit most when their therapeutic options are not restricted by the inappropriate use of evidence based studies.

I greatly appreciate your attention to this matter and for considering AfPA's perspective.

Sincerely,

Brian Kennedy
Executive Director

ALLERGAN

2525 Dupont Drive, P.O. Box 19534, Irvine, CA 92623-9534 (714) 246-4500

July 2, 2014

VIA Electronic Mail

Jeffrey A. Tice, MD
Daniel A. Ollendorf, PhD
Jed Weissberg, MD, FACP
Steven D. Pearson, MD, MSc
California Technology Assessment Forum
ctaf@icer-review.org

RE: Controversies in Migraine Management

Dear Drs. Tice, Ollendorf, Weissberg, and Pearson:

On behalf of Allergan Inc., the manufacturer of BOTOX® (onabotulinumtoxinA),[1†] I am submitting this correspondence in response to your request for comments regarding the above-captioned draft report and questions for deliberation. The draft report reviews the evidence on the "comparative clinical effectiveness and value" of four "new or controversial" therapies for migraine headache, including BOTOX® for the prophylaxis of headache in adult patients with chronic migraine. The questions for deliberation pose questions for the CTAF Panel to consider during its July 11, 2014 public meeting, including 2 voting questions (questions 3 and 4) regarding the use of BOTOX® for the prophylaxis of headache in adult patients with chronic migraine.

As explained in detail in our comments below, there are substantial and fundamental flaws in the economic analysis that supports the assessment of the comparative value of BOTOX® versus other therapies in the treatment of patients with chronic migraine. Therefore, we strongly urge CTAF to withdraw consideration of the report until such time as the flaws in the clinical evidence and economic model are addressed. The basis for this recommendation is provided below as responses to voting questions 3 and 4 (for ease of reference, your questions are reproduced below in bold text):

3. **For the prevention of chronic migraine, is the evidence adequate to demonstrate that the net health benefits of Botox injections used on an every 12 week schedule are superior to no treatment?**

Summary response: Yes. When BOTOX® is administered for the prophylaxis of headaches in adult patients with chronic migraine, and the product is administered in a manner consistent with the product's instructions for use, the published evidence supports a determination that the net health benefit of BOTOX® is superior to no treatment.

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[1] **WARNING: DISTANT SPREAD OF TOXIN EFFECT**
Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses. ***[See Warnings and Precautions (5.2)]***

Detailed response: In section 6.3 of the draft report, CTAF states that "[g]iven the demonstrated adverse events caused by botulinum toxin and the uncertainty about whether the observed clinical benefits are due to unblinding, there is moderate certainty that the net health benefits of [BOTOX® for the treatment of chronic migraine] are small, at best." We respectfully request that you reconsider this conclusion for the following reasons:

- **Patients treated with BOTOX® in the PREEMPT clinical trials experienced statistically and clinically significant improvements.** The headache-related burden and disability in individual patients with CM is multifaceted, encompassing headache frequency, duration, and severity. Therefore, the net health benefits of a treatment for patient with chronic migraine must consider multiple clinical endpoints and the impact on patient-centered outcomes. The PREEMPT studies demonstrate that prophylactic treatment with BOTOX® in patients with chronic migraine resulted in sustained, significant, and meaningful improvements from baseline across multiple headache symptom measures, including frequencies of headache days, headache episodes, migraine days, migraine episodes, moderate/severe headache days, and total cumulative hours of headache. The clinical significance of this improvement is evidenced by the statistically significant reductions observed favoring BOTOX® (versus placebo) in headache-related disability, resulting in significantly improved functioning, vitality, and overall health-related quality of life.[2]

- **BOTOX® treatment in adult patients with chronic migraine resulted in statistically significant and clinically meaningful improvements on both the HIT-6 and MSQ patient-reported outcomes measures in the PREEMPT trials.** The draft report concludes (at p. 29) that although the between group difference on the HIT-6 questionnaire is statistically significant, the difference is only minimally significant clinically. The reference cited to support this conclusion (Smelt *et al*, 2014) involved a primary care migraine population. A minimum clinically meaningful change threshold in a primary care migraine population is not relevant to inform what is a minimum clinically important change score for the severely disabled adult population with chronic migraine. The PREEMPT studies considered a change score of 2.3 units on the HIT-6 questionnaire to be clinically meaningful, as established by Coeytaux, *et al*. (2006)[3] in a study in a more severe population of patients with chronic daily headache. With respect to patient-centered outcome results in the PREEMPT trials, Aurora, *et al*. (2011)[4] concluded:

  > *OnabotulinumtoxinA treatment reduced headache-related disability and improved functioning, vitality, and psychological distress as measured by HIT-6. By the end of the double blind phase, the mean change from baseline in HIT-6 scores exceeded the established clinically meaningful between-group minimally important difference (MID) of 2.3 at week 24.In the OL phase, during which all patients were treated with*

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[2] Aurora SK, Dodick DW, Turkel CC, DeGryse RE, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 2010;30(7):793-803; Diener HC, Dodick DW, Aurora SK, Turkel CC, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 2010;30(7):804-814.

[3] Coeytaux RR, Kaufman JS, Chao R, *et al*. Four methods of estimating the minimal important difference score were compared to establish a clinically significant change in Headache Impact Test. *J Clin Epidemiol*. 2006 Apr;59(4):374-80.

[4] Aurora SK, Winner P, Freeman MC, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache.* 2011 Oct;51(9):1358-73.

onabotulinumtoxinA, continued improvements in the percent of patients with severe HIT-6 scores favoring patients treated early in the study were observed.

In addition, the report omits the PREEMPT results for the Migraine-Specific Quality of Life Questionnaire (MSQ), which complement and expand the patient-reported outcomes findings reported for the HIT-6. For the MSQ, BOTOX® treatment compared to placebo resulted in statistically significant and clinically meaningful improvements across multiple domains. These results are reported by Lipton, *et al* (2011)[5] and by Aurora, *et al*. (2011)[6]. With respect to the MSQ, Aurora stated:

Clinically significant improvements in HRQoL were observed at week 24 for all 3 role function MSQ domains, where onabotulinumtoxinA treatment (role restrictive [RR] 8.4, role preventive [RP] 6.7,and emotional functioning [EF] 8.4) far exceeded the previously established between-group MIDs (RR 3.2, RP 4.6,and EF 7.5) [cite: Cole JC, Lin P, Rupnow MF. Minimal important differences in the Migraine-Specific Quality of Life Questionnaire (MSQ) version. Cephalalgia. 2009; 29:1180-1187] compared to placebo at the end of the DB phase (week 24). Additionally, the established within-group MIDs (RR 10.9, RP 8.3, and EF 12.2) [cite: Dodick DW, Silberstein S, Saper J, et al. The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache. 2007;47: 1398-1408.] were also exceeded for onabotulinumtoxinA treatment but not for placebo at week 24 (Table 2). In the OL phase, after all patients were treated with onabotulinumtoxinA, continued improvements from baseline in HRQoL, as assessed by all 3 role function domains of the MSQ, were observed for all patients. The multiple variables assessed in PREEMPT and the statistically significant results are in alignment with the IMMPACT paradigm and demonstrate clinically meaningful benefit of treatment with onabotulinumtoxinA in adults with CM.

- **BOTOX® was well-tolerated in the PREEMPT trials.** The draft report's Table 5 identifies muscle weakness, neck pain, neck stiffness, drooping eyelid and paresthesia as adverse events observed in randomized trials of botulinum toxin for the prevention of migraine headaches that were likely associated with active treatment. However, with the exception of paresthesia, Table 5's reported percentage of patients experiencing these adverse events is substantially larger than the adverse event rates reported in the double-blind and open-label phases of the PREEMPT trials, respectively:

Adverse event	Rate Reported in Draft Assessment (vs. placebo) (n=variable depending on indication and treatment arm)	Rate Reported During Double-Blind Phase of PREEMPT Trials (vs. placebo) (n=687 BOTOX®; 692 placebo)	Rate Reported During 32-Week Open-Label Phase of PREEMPT Trials (n=1,205)

[5] Lipton RB, Varon SF, Grosberg B, Goadsby PJ, DeGryse RE, Turkel CC. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology* 2011 Oct 11;77(15):1465-1472

[6] Aurora SK, Winner P, Freeman MC, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache.* 2011 Oct;51(9):1358-73

Adverse event	Rate Reported in Draft Assessment (vs. placebo) (n=variable depending on indication and treatment arm)	Rate Reported During Double-Blind Phase of PREEMPT Trials (vs. placebo) (n=687 BOTOX®; 692 placebo)	Rate Reported During 32-Week Open-Label Phase of PREEMPT Trials (n=1,205)
Any adverse event	57% (vs. 46%)	29.4% (vs. 12.7%)	20.3%
Muscle weakness	21% (vs. 2%)	5.5% (vs. 0.3%)	3.9%
Neck pain	19% (vs. 4%)	6.7% (vs. 2.2%)	4.6%
Neck stiffness	14% (vs. 4%)	2.3% (vs. 0.7%)*	1.7%
Drooping eyelid	8% (vs. 1%)	3.3% (vs. 0.3%)	2.5%
Parasthesia	3% (vs. 1%)	3.2% (vs. 2.0%)**	2.0%

*Figures represent reports of "musculoskeletal stiffness" during PREEMPT trials
**Figures represent reports of "injection-site pain" during PREEMPT trials

The rates reported in the draft assessment appear to be supported by a 2012 meta-analysis.[7] Please note, however, that in calculating the above-referenced figures, the authors of the meta-analysis included adverse event reports from studies in patients (a) diagnosed with a type of headache other than chronic migraine (i.e., episodic migraine, chronic daily headache, or chronic tension-type headache), and (b) administered BOTOX® in a manner that is not consistent with the injection paradigm set forth in the BOTOX® package insert. A total of nine exploratory studies were initiated by Allergan from 1997 to 2001 that provided information to establish the optimal dose and injection paradigm for BOTOX® in the treatment of chronic migraine to maximize safety and efficacy, which informed the dosing used in the PREEMPT trials. In the BOTOX® package labeling, the recommended dosing consists of 155 U of BOTOX® administered to 31 injection sites across 7 head and neck muscles using a fixed-site, fixed-dose (FSFD) injection paradigm. Results from studies in non-chronic migraine patients and/or which do not employ the PREEMPT dosage and injection paradigm cannot be used to assess the current safety and efficacy of BOTOX® for the treatment of chronic migraine.

Because chronic migraine patients are severely disabled, virtually any improvement in headache symptom(s) is likely to be considered a clinically meaningful improvement. As such, notwithstanding the occurrence of any adverse events, patients reported clinically significant improvements in multiple headache symptom measures and patient-reported health-related quality of life endpoints, including the HIT-6 and MSQ, during the PREEMPT trials.

- **Clinical evidence suggests blinding was maintained during the PREEMPT trials.** Placebo patients were injected in the same pattern and in the same volume as patients treated with BOTOX®. Dodick *et al.* summarize the evidence that the blind was maintained as follows:

[7] Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: A meta-analysis. *JAMA* 2012;307(16):1736-1745.

> *In these studies, there was a risk that patients and/or investigators may have been unblinded to the study treatment because of the physical changes that may have occurred due to muscle relaxation in the forehead of patients treated with onabotulinumtoxinA. Although this could have contributed to an enhanced active response, it is at odds with a high placebo response and the absence of a parallel nocebo effect. If placebo patients had "seen" the absence of physical changes in foreheads, then they would have been equally unblinded to placebo treatment. Thus, a low placebo response would have been expected. Furthermore, AEs that are known to occur after treatment with onabotulinumtoxinA due to the pharmacologic effects, such as local muscle weakness manifested as ptosis, were reported in patients who were treated with placebo. Indeed, the presence of the placebo response suggests that the blind was maintained.*[8]

a. <u>If yes, what is the comparative value of Botox injections vs. no treatment (low, reasonable, high)?</u>

<u>Summary response</u>: When BOTOX® is administered for the prophylaxis of headaches in the severely debilitated population of adult patients with chronic migraine, and the product is administered in a manner consistent with the product's instructions for use, the preponderance of published, evidence supports a determination that the comparative value of BOTOX® is high. In addition, the economic model in the draft report, once corrected for fundamental and serious errors, also strongly supports that BOTOX® is of high value, resulting in better outcomes vs. no treatment and only slightly higher costs.

We replicated the model described in the draft report and found several fundamental and serious errors including: (1) over estimation of BOTOX® costs by 81%, (2) the erroneous inclusion of "Placebo" effectiveness for the "No Therapy" comparator group, (3) the failure to include a cost for "Placebo" injection treatment while including effectiveness for Placebo, and (4) the inclusion of patients with episodic migraine.

<u>Detailed response</u>: In section 7.4 of the draft report, CTAF summarizes the results of an economic model it developed to assess the potential costs and cost-effectiveness of BOTOX® vs. no therapy for the treatment of chronic migraine, and concludes that BOTOX® "would need to reduce headache frequency from 20 to 3 days per month to completely offset the additional intervention costs." As explained in detail below, we have a number of methodological concerns about the model that enabled CTAF to reach this conclusion:

- **The model over-estimates the cost of BOTOX® by a significant margin.** Medi-Cal pays $5.45 per Unit of BOTOX®. The model, however, assumes a cost of $9.91 per Unit. As explained below, the $9.91 rate only applies to the first Unit;[9] the remaining 199 Units are reimbursed at $5.45 per Unit ($9.91 - $4.46):

  > *Reimbursement is determined by the cost of the injection, plus the physician's injection administration fee for the first billed unit of drug.* ***The price listed on the Medi-Cal Rates page of the Medi-Cal website for each Physician-***

[8] Dodick DW, Turkel CC, DeGryse RE, Aurora SK, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. *Headache* 2010;50:921-936.

[9] California Department of Health Care Services, Medi-Cal Rates Information (June 15, 2014), http://files.medi-cal.ca.gov/pubsdoco/rates/rates_information.asp?num=23&first=A0030&last=L3253.

> ***Administered Drug includes the one-time injection administration fee of $4.46. Since the injection administration fee is applied only once for each drug administered, subsequent units claimed will have the administration fee subtracted from the published rate.***[10]

As illustrated below, the inclusion of the administration fee in the cost estimate for the full 200 Units results in an over-estimate of the actual cost of BOTOX® by 81-percent:

	CTAF Model	**Actual Medi-Cal Rate**	**Difference**
Estimated Units per treatment[11]	200 U	200 U	
Estimated cost per Unit	$9.91	$9.91 (for first Unit); $5.45 (for remaining Units)	
Estimated cost per treatment	$1,982.00	$1,094.46	($887.54)
Annual estimated cost per patient (assuming 4 treatments per year)	$7,928.00	$4,377.84	($3,550.16)

(Note: The model does not account for the cost of the BOTOX® injection procedure, which is reported using CPT code 64615 "Chemodenervation of muscle(s); muscles innervated by facial, trigeminal, cervical spinal and accessory nerves, bilateral (eg, for chronic migraine)". The Medi-Cal reimbursement rate for 64615 is $103.87.[12] If the cost of the injection procedure is incorporated into the "Actual Medi-Cal Rate" column of the above table, the estimated cost per treatment rises to $1,198.33 ($4,793.32 per year, assuming 4 treatments per year); nevertheless, the model continues to significantly over-estimate the cost of BOTOX® (by approximately 81%).

We replicated the model and all results described in the economic analysis section in the draft report. In all instances below for reporting results with an updated model, it is for the scenario of a cohort of adult patients with chronic migraine of 20 headache days per month at model entry (day 0), this is consistent with the baseline characteristic of the PREEMPT study population.

When the model is corrected with the actual Medi-Cal cost for BOTOX® and inclusion of the cost of the injection procedure for both BOTOX® and Placebo comparators, the incremental cost per headache day avoided for BOTOX® vs Placebo is $157 (reduced from $287 in the draft CTAF

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[10] California Department of Health Care Services, Provider Manuals – General Medical (GM), Injections: An Overview, at 1, https://files.medi-cal.ca.gov/pubsdoco/publications/masters-mtp/part2/injectanover_m00o03o04o11p00.doc (last visited June 25, 2014).

[11] Per section 2.4 of the BOTOX® PI, the recommended dose of BOTOX® for the treatment of chronic migraine is 155 Units. BOTOX® is available in single-use 100 Unit and 200 Unit vials. As such, a provider that administers 155 Units of BOTOX® in a manner consistent with the product's instructions for use will have 45 Units left over at the end of the procedure. Medi-Cal rules allow a provider to bill for unavoidably wasted BOTOX®. *See* California Department of Health Care Services, Provider Manuals – General Medical (GM), Injections: Drugs A-D Policy, at 1, http://files.medi-cal.ca.gov/pubsdoco/publications/masters-mtp/part2/injectdruga-d_m00o03o04o11p00.doc (last visited June 25, 2014).

[12] California Department of Health Care Services, Medi-Cal Rates Information (June 15, 2014), http://files.medi-cal.ca.gov/pubsdoco/rates/rates_information.asp?num=16&first=63285&last=67107.

report). Similarly, the cost per headache day avoided for BOTOX® vs No Therapy is $18 (reduced from $147 in the draft report).

- **The effectiveness of the Placebo comparator group is erroneously conferred on the No Therapy group.** In replicating the model and all results described for the economic analysis in the draft report, the only way to obtain the results presented in Figure 4 (p. 43) for No Therapy, was to assume the same effectiveness for No Therapy as for the Placebo group. That is, the only way to replicate the cost per headache day avoided for BOTOX® vs Placebo of $147 (for patients with 20 headache days at baseline) as reported in Figure 4, was to assume 159,000 headache days per year for the No Therapy cohort, which is actually the number reported for the Placebo group in Table 11 on page 42. When this is corrected to the accurate number of 240,000 headache days per year for the No Therapy group, along with the correction in actual BOTOX® and procedure costs, the cost per headache day avoided for BOTOX® vs No Therapy is reduced from $147 in the draft report to $4.

- **The economic model does not account for the procedure cost associated with Placebo.** The economic model does not account for both the effectiveness and the expected costs, that would be associated with Placebo treatment as determined from the PREEMPT study. Rather, it includes only the effectiveness of Placebo as observed in PREEMPT, but not the costs. To adequately and reasonably model the resources associated with Placebo treatment as defined in PREEMPT, the economic model should include a cost for the physician time, skill, and materials associated with 31 fixed-site intramuscular injections across 7 specific head/neck muscle areas for Placebo in each treatment cycle.

  Including the same physician injection fee associated and reimbursed by Medi-Cal for BOTOX® ($103.87 per treatment cycle) into the model, and correcting with the actual Medi-Cal cost for BOTOX® and inclusion of the injection procedure for BOTOX®, the cost per headache day avoided for BOTOX® vs Placebo is reduced from $287 (draft CTAF report) to $140 (revised, corrected model).

- **The model includes patients with episodic migraine.** The model includes cost estimates for patients that experience 5, 10, 15 and 20 headache days per month, respectively. However, BOTOX® is only FDA-approved for the treatment of patients with chronic migraine (i.e., at least 15 headache days per month); the product's labeling explicitly states that the "[s]afety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month)".[13] By including patients with fewer than 15 headache days per month, the model estimates the cost of BOTOX® for the treatment of a population for which the safety and efficacy of BOTOX® have not been established.

In addition to the fundamental and serious errors listed above for the economic model in the draft report, there are additional concerns with the model:

- **The effectiveness measure in the economic analysis is limited to headache days as a measure of effectiveness and does not consider other important aspects of value from other headache measures and patient-reported outcomes.** The headache-related burden and disability in individual patients with CM is multifaceted, encompassing headache frequency, duration, and severity. Therefore, any assessment of the value of BOTOX® treatment must also consider

[13] BOTOX® (onabotulinumtoxinA) package insert, § 1.2 (last revised February 2014).

additional health benefits of a treatment for patients with chronic migraine including consideration of multiple endpoints and the impact on patient-centered outcomes. We recommend that in addition to a corrected assessment of cost per headache days avoided, that the additional health benefit demonstrated on health-related quality of life, as earlier referenced to Aurora, *et al*. (2011)[14] and Lipton, *et al*. (2011),[15] also be considered as part of a comprehensive and evidence-based assessment of value.

- **The analysis by CTAF does not include potential resource use and cost offsets associated with BOTOX® treatment.**

  Chronic migraine patients are severely debilitated and clinically meaningful improvements in their symptoms (even small) may be postulated to reduce costly headache-related medical resources (e.g., emergency department visits). Recent real-world research assessing medical resources use pre-vs. post initiation of BOTOX® treatment for patients with chronic migraine and treated according to the PREEMPT injection paradigm have reported such benefits.

  In a recent case series of 230 patients completed by Rothrock and colleagues (manuscript submitted and under review), 42% relative reductions in headache-related ER visits were observed comparing the pre-vs.post 6-month period of initiating BOTOX® treatment. A 53% reduction in headache-related hospitalization was observed. (this manuscript will be provided upon request).

  Based on the findings in the Rothrock and colleague case series, Allergan initiated a claims database analyses using the TRUVEN MarketScan Databases® to investigate the headache-related resource utilization (ER visits, hospitalizations, and acute medication use) among patients with chronic migraine pre and post-BOTOX® treatment. The analysis cohort included 1,795 patients with chronic migraine treated with BOTOX® through 2012 , who met pre-specified inclusion criteria including: receiving medical and pharmacy coverage continuously during wash out, 6-month pre-index, and 6-month post index periods; and have no greater than 120 days between BOTOX® injection, resulting in each patient having at least 2 cycles of BOTOX® treatment during the 6-month follow-up periods. Compared to the 6-month pre-index prior to initiating BOTOX® treatment, a statistically significant relative reduction in headache-related ER visits of 35% was observed in the 6-month period post BOTOX® treatment initiation compared to the 6-month pre-period without BOTOX® treatment. Similarly, a statistically significant 47-percent relative reduction in headache-related hospitalizations was observed in the 6-month period post BOTOX® treatment initiation compared to the 6-month pre-period without BOTOX® treatment . Lastly, the number of patients with $\geq$1 medication claim for acute medications was improved (reduced) comparing the pre- versus post-BOTOX® treatment periods. Statistically significant reductions were observed of 6.1% among patients receiving triptans, 5.4% among patient receiving barbiturates, and 1.9% among patients receiving NSAIDS in the pre-BOTOX® treatment periods. Trends of improvements (reduction), although not meeting statistical

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[14] Aurora SK, Winner P, Freeman MC, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. *Headache.* 2011 Oct;51(9):1358-73

[15] Lipton RB, Varon SF, Grosberg B, Goadsby PJ, DeGryse RE, Turkel CC. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology* 2011 Oct 11;77(15):1465-1472

significance, were also observed of 1.5% each for patients receiving opioids and muscle relaxants, respectively.

- **The analysis suggests CTAF may not recommend the use of BOTOX® unless the therapy is shown to be cost-saving or cost-neutral.** This is an unsubstantiated position taken in the draft report and it is unclear why CTAF would consider BOTOX® not to be of high value unless it is cost-neutral or cost-saving. This suggestion is inconsistent with well-established principles for health technology assessment and cost-effectiveness analysis. According to Gold et al (1996)[16] in their classic text (p. 27), cost effectiveness analysis is typically performed in circumstances when the intervention is both more costly and more effective than alternative interventions. "Interventions that have a relatively low C/E ratio are 'good buys' and would have high priority for resources."

- CTAF's focus on cost-neutrality also ignores the sustained, clinically-significant improvements that BOTOX®-treated patients experience across multiple headache symptom measures, as evidenced by measures indicating a significant improvement in functioning, vitality, and overall health-related quality of life.

In summary, using the results of the revised model, as presented above, the cost-per headache day avoided with BOTOX® may be as low as $140 when compared with placebo or $4 when compared with no treatment. In order to assess the value of BOTOX® in the treatment of patients with chronic migraine, one must consider what cost thresholds per headache day avoided represent high, moderate, or low value. We are not aware of any published references for such thresholds. Such thresholds can appropriately be determined by assessing the willingness-to-pay (from the perspective of the relevant population, such as Medi-Cal beneficiaries or Californians as a whole). Unless those who conducted the analysis presented in the CTAF report are aware of a published reference threshold or until a willingness-to-pay study is conducted to determine such thresholds, we question how CTAF could conclude that the relatively modest costs-per headache day avoided—especially when considering the substantial disability represented by a headache day in patients with chronic migraine—is anything other than high value.

4. **For the prevention of chronic migraine, is the evidence adequate to demonstrate that the net health benefits of Botox injections used on an every 12 week schedule are equivalent to those of other preventive medications?**

Summary response: The evidence regarding the safety and efficacy of the selected comparator medications (topiramate and amitriptyline) is not sufficiently developed to allow for the assessment of whether the net health benefit of BOTOX®, when administered for the prophylaxis of headaches in chronic migraine and consistent with the product's instructions for use, is equivalent to such comparator medications.

Detailed response: In section 6.3 of the draft report, CTAF states that "the evidence is insufficient to assess the net health benefits for botulinum toxin compared to established preventative therapies". This statement is accurate, but only because there is insufficient evidence from which to evaluate the CTAF-identified comparators – amitriptyline and topiramate – in the prophylaxis of headaches in patients with chronic migraine. To date, there is no clinical trial comparing the safety and efficacy of BOTOX® to amitriptyline in the prophylaxis of chronic migraine. Specifically, the model assumes that there are "no

[16] Gold M, Siegel JE, Russel LB, *et al*. *Cost-effectiveness in health and medicine*. New York: Oxford University Press; 1996.

differences in effectiveness between BOTOX® and amitriptyline" in the prophylactic treatment of chronic migraine. However, the small (n=72), ex-U.S. study that CTAF cites to support this assumption is a trial that compares the efficacy of amitriptyline with DYSPORT® (abobotulinumtoxinA) – not BOTOX® (onabotulinumtoxinA) – for the treatment of chronic daily migraine. (Written confirmation received from the lead author that the study involved the use of DYSPORT® in the above-described clinical trial.) Although both are type A botulinum toxin products, BOTOX® and DYSPORT® are not interchangeable. Moreover, as noted in section 2.1 of the BOTOX® package insert, the units of biological activity of BOTOX® cannot be compared to nor converted into units of any other botulinum toxin product. The products are biochemically, physically, and clinically distinct, and differ in terms of source cell line, manufacturing process, complex size, uniformity, and excipients. BOTOX® and DYSPORT® have unique lists of FDA-approved indications, and BOTOX® is the only botulinum toxin product that is FDA-approved for the treatment of chronic migraine. Evidence regarding the safety and efficacy of BOTOX® in the treatment of chronic migraine cannot be extrapolated to DYSPORT® (or vice-versa). Specifically, one cannot assume that the dosage and regimen of DYSPORT® used in the study of DYSPORT® versus amitriptyline is one that would be expected to show clinical benefit in the management of patients with chronic migraine. It required approximately 10 years of clinical study with BOTOX® before a promising treatment regimen in chronic migraine was identified that was then investigated in the Phase III clinical trials.

There are only two clinical trials that have directly compared the safety and efficacy of BOTOX® and topiramate in the prophylaxis of chronic migraine. In these two trials, each involved relatively small numbers of patients (in the largest study, n=59) and neither investigated the effectiveness of BOTOX® when administered consistent with the dosage and injection paradigm set forth in the package labeling (based upon the PREEMPT randomized, controlled trial data). As such, these comparative studies do not provide evidence of sufficient quality to assess the comparative safety and efficacy of BOTOX® and topiramate for the treatment of chronic migraine, nor do they reflect the manner in which BOTOX® is currently used in clinical practice.

There is sufficient basis, however, to question CTAF's characterization of topiramate and amitriptyline as "established preventive therapies" for the prophylaxis of chronic migraine. We acknowledge that the American Academy of Neurology (AAN) supports the use of topiramate and amitriptyline in its 2012 evidence-based guidelines for the prophylaxis of episodic migraine.[17] Chronic migraine does not refer to patients that have a long history of episodic migraine. Rather, episodic migraine is a condition that differs from chronic migraine with respect to epidemiologic and symptom profiles, functional consequences and disabilities, indirect and direct costs, patterns of consultation and treatment, and rates of comorbidities.[18] Indeed, while the BOTOX® package insert supports use of the product for the prophylaxis of chronic migraine, the PI clearly states that "[s]afety and effectiveness [of BOTOX®] have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies". Katsarava *et al*. recently explained:

> *Most headache clinicians agree that acute episodic migraine and chronic migraine differ in their pathophysiology, etiology, diagnosis, and response to pharmacological as well as nonpharmacological therapies. While acute pain is often described as transient, self-limiting, and serves a protective biological*

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[17] *See* Silberstein SD, Holland S, Freitag F, Dodick DW, *et al*. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. *Neurology* 2012;78:1337-1345.

[18] Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep* 2012;16:86-92.

> *function, chronic pain is not thought to serve a protective function but leads to neuroplastic tissue changes, and becomes detrimental to overall health. Another major difference between episodic and chronic migraine is that while episodic migraine attacks can often be effectively treated, chronic migraine is more refractory or its response is more muted to commonly used antimigraine treatments, including the triptans*[19]

Moreover, as physician "understanding of the clinical, epidemiological, and pathophysiological differences between EM and CM develops, it becomes highly likely that we will find the patterns of treatment response to preventive therapies to be different between the two migraine groups".[20] Because chronic migraine and episodic migraine are distinct clinical conditions, it is clinically inappropriate to use evidence from patients with episodic migraine to assume any particular treatment effect for patients with chronic migraine.

The evidence supporting the use of topiramate or amitriptyline in the prophylaxis of headaches in patients with chronic migraine is limited. For example:

- **Neither product is FDA-approved for the treatment of chronic migraine.** Amitriptyline is not FDA-approved for the prophylaxis of any type of headache, including chronic migraine. Topiramate is FDA-approved for the prophylaxis of migraine headache, but not specifically for chronic migraine. The Level A and B evidence on use of anticonvulsants and antidepressants in prophylactic migraine treatment have involved episodic migraine populations, not chronic migraine patients (refer to AAN Practice Parameters for Episodic Migraine)[21]

- **Publications detailing the randomized, placebo-controlled trials that purport to support the use of the products in the treatment of chronic migraine are subject to significant limitations.** For example, in a randomized, placebo-controlled, parallel-group, multicenter trial (n=328), Silberstein *et al*. concluded that chronic migraine patients experienced "significant reductions in the mean monthly number of migraine/migrainous days and the mean number of migraine days" following therapy with topiramate. Forty-four percent in both topiramate and placebo groups did not complete the study. Most common reason for discontinuation was inadequate efficacy (topiramate =12.7% and placebo = 18.4%). Discontinuation rates due to adverse events were 10.9% for topiramate and 6.1% for placebo groups. The mean duration of therapy was just 91.7 ± 34.7 days for the topiramate group (vs. 90.6 ± 34.8 days for the placebo group), and only 55.8% (92/165) of topiramate-treated patients and 55.2% (90/163) of placebo-treated subjects completed the trial. Moreover, treatment-related adverse events were reported by 65.0% of topiramate-treated patients (vs. 42.9% in the placebo treated group); the most commonly reported treatment-related adverse events in the topiramate group (vs. placebo) were paresthesia (28.8% (vs. 7.5%)), fatigue (10.6% (vs. 9.3%)), difficulty with concentration (9.4% (vs. 2.5%)), dry mouth (6.2% (vs. 2.5%)), and nausea (6.2% (vs. 6.3%)).[22]

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[19] Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep* 2012;16:86-92

[20] Durham PL, Cady R. Insights into the mechanism of onabotulinumtoxinA in chronic migraine. *Headache* 2011;51:1573-1577..

[21] *See* Silberstein SD, Holland S, Freitag F, Dodick DW, *et al*. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. *Neurology* 2012;78:1337-1345.

[22] Silberstein SD, Lipton RB, Dodick DW, Freitag FG, *et al*. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. *Headache* 2007;47:170-180.

Similarly, as part of a larger double-blind, placebo-controlled study (n=391), Couch *et al*. performed a sub-group analysis (n=58) that concluded amitriptyline was "statistically significantly superior to placebo at 8 weeks and 16 weeks with a similar but nonsignificant trend at 12 and 20 weeks" in patients with chronic daily headache (≥ 17 headache days per month). Discontinuation and adverse event rates were not separately reported for patients with chronic daily headache. In the study population as a whole, though, 48% (93/194) of amitriptyline and 54% (106/197) of placebo patients discontinued the study before 20 weeks, and the major individual adverse events for which there were significant differences in occurrence between groups included dry mucous membranes, constipation, urinary retention, dizziness, and somnolence.[23]

a. <u>If yes, what is the comparative value of Botox injections vs. other preventive medications (low, comparable, high)?</u>

<u>Summary response</u>: The comparative value of BOTOX® and amitriptyline in the prophylaxis of chronic migraine cannot be assessed because no published clinical trial – including the trial cited in the model – directly compares the safety and efficacy of BOTOX® and amitriptyline in the treatment of patients with chronic migraine.

<u>Detailed response</u>: In section 7.4 of the draft report, CTAF summarizes the results of an economic model it developed to assess the potential costs and cost-effectiveness of BOTOX® and amitriptyline for the treatment of chronic migraine, and concludes that "at the reimbursement levels assumed in [the cost-effectiveness] analysis, there [is] no [efficacy] threshold at which BOTOX® would be considered cost-neutral; the cost per headache day averted would still be $12 even if BOTOX® were assumed to eliminate all headaches." However, in addition to the methodological issues we identified in response to question 3(a) – which are also applicable to the model's assessment of BOTOX® and amitriptyline – we are concerned that the model relies on a study that compares amitriptyline and DYSPORT® to support its comparison of amitriptyline and BOTOX®.[24]

In conclusion, there are substantial and fundamental flaws in the economic analysis: (1) cost/year of BOTOX® is 81-percent higher than the true Medi-Cal rate, (2) comparative data from which the model assumed no difference in benefit from treatment with BOTOX® is taken from a study comparing amitriptyline versus DYSPORT® (abobotulinumtoxinA)--not BOTOX® (onabotulinumtoxinA), (3) amitriptyline is not widely recommended for treatment of chronic migraine and is not, therefore, an appropriate comparator for a cost-effectiveness analysis, (4) neither downstream cost-offsets nor benefits in patient-reported outcomes from BOTOX® are included in the model. These flaws should preclude CTAF's making any conclusions about the value of treatment of chronic migraine with BOTOX®. We strongly urge CTAF to withdraw consideration of the report on BOTOX® in the treatment of chronic migraine until such time as the flaws in the clinical evidence and economic model as summarized in this letter are addressed.

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[23] Couch JR. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. *Headache* 2011;51:33-51.

[24] Notwithstanding the fact that the model in the report is based upon DYSPORT, rather than BOTOX, and uses amitriptyline as a comparator, which has not been shown to be comparable to BOTOX in chronic migraine, if one applies the model using the correct Medi-Cal cost for BOTOX®, the cost per headache day avoided versus amitriptyline drops from $920 to $538. Moreover, accounting for published persistency rates for amitriptyline in RCTs of 54.9% (Hepp, *et al*. (2014)) and adjusting those for BOTOX to 89.6% due to all causes in PREEMPT, the costs per headache day avoided versus amitriptyline drop from $920 to $77.

* * * * * * * * * *

I hope that you have found these comments to be helpful and informative. If you have any questions, please do not hesitate to contact Karen Campbell, PharmD for clinical questions at 949-677-1512 or via e-mail at Campbell_Karen@allergan.com and Jonathan Kowalski, PharmD, VP US Health Outcomes for pharmacoeconomic question at 949-246-6316 or via email at Kowalski_Jonathan@allergan.com.

Regards,

Karen Campbell and Jonathan Kowalski

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† The current package labeling includes the following indications for BOTOX®:

1.1 Bladder Dysfunction

Overactive Bladder

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Detrusor Overactivity associated with a Neurologic Condition

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

1.2 Chronic Migraine

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

Important limitations

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

1.3 Upper Limb Spasticity

BOTOX is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor digitorum sublimis).

Important limitations

Safety and effectiveness of BOTOX have not been established for the treatment of other upper limb muscle groups, or for the treatment of lower limb spasticity. Safety and effectiveness of BOTOX have not been established for the treatment of spasticity in pediatric patients under age 18 years. BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens.

1.4 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.5 Primary Axillary Hyperhidrosis

BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Important limitations

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

1.6 Blepharospasm and Strabismus

BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

In addition, BOTOX® Cosmetic, which has distinct labeling, packaging and NDC-coding, has been approved by the FDA for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients, and for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients. (See Tab A for a copy of the BOTOX® package insert.)

ALLERGAN

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July 22, 2014

VIA Electronic Mail

Jeffrey A. Tice, MD
Daniel A. Ollendorf, PhD
Jed Weissberg, MD, FACP
Steven D. Pearson, MD, MSc
California Technology Assessment Forum
ctaf@icer-review.org

RE: Controversies in Migraine Management

Dear Drs. Tice, Ollendorf, Weissberg, and Pearson:

On behalf of Allergan Inc., the manufacturer of BOTOX® (onabotulinumtoxinA),[1†] I am submitting this supplemental second correspondence in response to your request for comments regarding the above-captioned draft report and questions for deliberation. The draft report reviews the evidence on the "comparative clinical effectiveness and value" of four "new or controversial" therapies for migraine headache, including BOTOX® for the prophylaxis of headache in adult patients with chronic migraine. The questions for deliberation are those considered by the CTAF Panel during its July 11, 2014 public meeting, including the 2 revised voting questions (questions 3 and 4) regarding the use of BOTOX® for the prophylaxis of headache in adult patients with chronic migraine. These comments focus specifically on the questions considered by the CTAF Panel on July 11, 2014 and concerns we identified with respect to the evidence presented or reviewed by the CTAF Panel. These comments do not repeat points addressed in our earlier correspondence submitted on July 2, 2014, prior to the meeting.

Question 3: For patients who have inadequate relief with other preventive therapies for chronic migraine, is the evidence adequate to demonstrate that the net health benefits of Botox injections used on an every 12-week schedule are better than no treatment?

Summary response: Yes. When BOTOX® is administered for the prophylaxis of headaches in adult patients with chronic migraine, and the product is administered in a manner consistent with the product's instructions for use, the published evidence supports a determination that the net health benefit of BOTOX® is better than no treatment.

Detailed response: We respectfully request that you consider the information provided below in support of the July 11, 2014 CTAF panel's 100% "yes" vote (in addition to Allergan's first clinical response submitted electronically on July 2, 2014).

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[1] **WARNING: DISTANT SPREAD OF TOXIN EFFECT**
Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses. *[See Warnings and Precautions (5.2)]*

BOTOX® has established evidence with the largest trials (PREEMPT) ever conducted specifically in patients with chronic migraine.[2] BOTOX® has not only demonstrated significant reduction in headache (HA) days (9.2 vs. 6.7 placebo), but across multiple headache symptom measures, including a reduction in total cumulative HA hours (132 vs. 90 placebo), reduced HA severity and HA-related disability compared to placebo. The net health benefits of BOTOX® cannot be measured from a single endpoint, but require consideration of a number of endpoints. When considering "no treatment" as a comparator, as posed in Question 3, it is important to understand that the effectiveness of "no treatment" cannot be inferred from the effectiveness of placebo injection in the clinical trials—i.e., it cannot be assumed that "no treatment" will produce a reduction of 6.7 HA days per month for all chronic migraine sufferers.

PREEMPT data support use of BOTOX® both in patients who have and who have not tried alternative therapies for treatment of chronic migraine prior to treatment with BOTOX®:

- During the July 11, 2014 CTAF public meeting there was discussion that ~60% of PREEMPT study patients had prior use of oral medications for headache prevention. Overall, 63.5% of enrolled subjects (61.8% BOTOX® and 65.2% placebo) had a history of prior headache prophylaxis medications use. The majority of patients who had taken prior headache prophylaxis medication discontinued due to lack of efficacy (56.9%) or an adverse effect (35.5%).[3]

- In the PREEMPT studies, the definition of prior oral medication use was very broad. In January 2006, at the time that the Allergan PREEMPT Phase 3 studies were initiated, there was no international and/or agreed upon local guidelines of "proven effective" migraine headache prophylaxis treatments. A list of >100 medications and herbal supplements identified by the lead coordinating investigators as medications known to be used for "headache prophylaxis" was used to categorize patients as having or not having used oral preventive therapies for migraine. Most of these listed treatments lack evidence-based controlled data in either episodic or chronic migraine subjects. Drugs included on this list were from the following classes: anticonvulsants, antidepressants, antihistamine and serotonin antagonists, antihypertensives, antipsychotics, beta blockers, calcium channel blockers, and various combination pain medications. In addition, dietary supplements (e.g., vitamins), herbs, minerals, hormonal, or combinations, ergot alkaloids, muscle relaxants, non-steroidal anti-inflammatory drugs (NSAIDs), and opioids were also included.

- Investigators were instructed to record the past use of any of the medications on the list whether or not the treatment was prescribed as headache prophylaxis. Furthermore, if a patient reported that s/he had taken any other headache prophylactic drug/herbal not listed, it was also to be recorded in the case report form.

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[2] Aurora SK, Dodick DW, Turkel CC, DeGryse RE, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia 2010;30(7): 793-803; Diener HC, Dodick DW, Aurora SK, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia 2010;30(7): 804-814.

[3] Allergan, Inc. Data on file and available upon request.

Table 1. Proportion of Subjects with Prior Headache Prophylaxis Medication Use in PREEMPT

Pooled 191622-079 + 191622-080 Studies[4]	BOTOX® (N=688)	Placebo (N=696)	Total (N=1384)
Allergan Phase 3 PREEMPT Studies Headache Prophylaxis Medication Guideline	425 (61.8%)	454 (65.2%)	879 (63.5%)

Source: Allergan, Inc. Data on file and available upon request.

The CTAF draft report states that "*Guidelines recommend that physicians discuss preventive therapy with patients suffering from two or more headaches per month that interfere with daily activities*." These recommendations include discussions for episodic migraine patients as well as chronic migraine patients. Insofar as BOTOX® is approved for and the clinical evidence supports its use for chronic migraine and not episodic migraine, it would appear appropriate to focus the report on evidence specific to the management of chronic migraine—not evidence on the management of episodic migraine.

The American Academy of Neurology's (AAN) Evidence-based Guidelines Update, Pharmacologic Treatment for Episodic Migraine in Adults, addressed the clinical question, "What pharmacologic therapies are proven effective for migraine prevention?" The report from the subcommittee provided Level A or Level B recommendations for some, but not all, of the agents reviewed for the prevention of episodic migraine.[5] We acknowledge that the AAN supports the use of topiramate and amitriptyline in its 2012 evidence-based guidelines for the prophylaxis of episodic migraine (A and B level evidence ratings for anticonvulsants, beta blockers, triptans (short-term menstrual related migraine) and B level evidence ratings for antidepressants). However, there is no such guideline recommendation for the use of prophylactic medications in chronic migraine.

Finally, BOTOX® is the only pharmacologic therapy approved by the FDA for the prevention of chronic migraine.

In summary, the established evidence supports the panel's 100% "Yes" vote to Question 3, "For patients who have inadequate relief with other preventive therapies for chronic migraine, the evidence is more than adequate to demonstrate that the net health benefits of Botox injections used on an every 12-week schedule are better than no treatment?"

Question 3a: If yes, what is the comparative value of Botox injections vs. no treatment?

Summary Response: When BOTOX® treatment is administered for the prophylaxis of headaches in the severely debilitated population of adult patients with chronic migraine, and the product is administered in a manner consistent with the product's instructions for use, the preponderance of evidence produced by

[4] Dodick DW, Turkel CC, DeGryse RE, *et al*. PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010;50(6): 921–936.

[5] Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78: 1337-1345.

CTAF supports a determination that the comparative value of BOTOX® is **high**, resulting in better outcomes vs. no treatment and only slightly higher costs.

When question 3a was voted on at the July 11, 2014 meeting, the CTAF Panel vote resulted in a majority voting that the comparative value of BOTOX® treatment vs. no treatment is **low**. This vote appears to have been made without clear direction to the panel on the specific criteria and evidence to consider for their vote, including objective consideration of the evidence included in the CTAF draft report and data presented by CTAF at the meeting. Instead, the vote appears to have been a largely subjective determination because the available evidence clearly supports a **high** value determination. In addition, consideration of and correction to limitations in that data or presentation of data by CTAF further support the reasonable conclusion of high comparative value for BOTOX® treatment vs. no treatment in adult patients with chronic migraine.

Therefore, Allergan requests that CTAF/ICER reconsider the direction and quality of their voting process for future meetings, and that the final CTAF cost effectiveness model and the relevant report sections be updated to incorporate the evidence and transparent points outlined below.

Detailed Response: At the July 11, 2014 meeting, the CTAF panel voted unanimously for Q3 (100%; 11 of 11) that "yes" they considered the evidence provided by CTAF/ICER to be adequate to demonstrate the net health benefits of BOTOX® treatment used every 12-weeks are better than no treatment. However, the CTAF Panel voted for Q3a using the provided "value" grid as follows:

- 45% vote = 2 (low value)
- 18% vote = 3 (low value)
- 27% vote = 6 (reasonable value)
- 9% vote = 10 (high value)

Low Value	Reasonable/ Comparable Value	High Value
		7. Comparable outcomes; Lower cost
1. Comparable outcomes; Higher cost	4. Comparable outcomes; Comparable cost	8. Promising but inconclusive evidence of better outcomes; Lower cost
2. Promising but inconclusive evidence of better outcomes; Higher cost	5. Promising but inconclusive evidence of better outcomes; Comparable cost	9. Better outcomes; Lower or comparable cost
3. Better outcomes; Too high a cost	6. Better outcomes; Reasonable higher cost	10. Better outcomes; Slightly higher cost

Five panel members (45%; 5 of 11) specified a vote for cell 2 of the grid ("promising but inconclusive evidence of better outcomes; higher cost") but previously voted in Q3 that there was adequate evidence to demonstrate that the net health benefits of BOTOX® treatment are better than no treatment. Since the cost of BOTOX® per headache day averted was shown in the CTAF model to be greater than zero (i.e.,

"higher cost" than no treatment), voting a 2 on the grid for Q3a therefore would be solely based on "promising but inconclusive evidence," directly contradicting and internally inconsistent with the evidence and unanimous vote of adequate evidence of the net health benefit of BOTOX® established for question 3.

Two panel members specified a low value vote for Q3a with a vote of 3 ("better outcomes; too high a cost") for BOTOX® treatment versus no treatment. The revised cost effectiveness model results comparing BOTOX® treatment vs. no treatment (and correcting for cost and effectiveness parameter errors in the CTAF draft report and economic model) presented by CTAF/ICER at the July 11, 2014 meeting and included in Figure 4 of the handout provided at the meeting, estimate a base-case result of the cost per headache day averted for BOTOX® vs. "no treatment" of $4 and $19 for 20 and 15 baseline headache days per month, respectively. The vote of a 3 for Q3a ("better outcomes; too high a cost") means that those panel members concluded that the cost of BOTOX® is too high because if one did not believe BOTOX® had better outcomes than no treatment, then a vote of 1 or 2 would have resulted. It appears based on the voting results of Q3, the economic model results, and the Q3a voting results, that it was unclear to the panel members what evidence they were supposed to base their votes on. Using the revised economic model provided by CTAF/ICER, how could one reasonably conclude that a cost of $4 or $19 per headache day averted for BOTOX® treatment vs. not treatment is "too high a cost"?

In addition, there was also relevant expert testimony from headache specialists at the meeting stating that, in their clinical experience, BOTOX® treatment resulted in especially strong effectiveness for some patients that could not be reliably predicted *a priori*, a real-world practice observation also supported by the results of PREEMPT. In the 24-week double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program, a significantly greater percentage of BOTOX®-treated compared to placebo-treated patients had at least a 50% decrease from baseline in the frequency of headache days at all-time points, starting at the first post-treatment study visit (week 4) and including week 24 (BOTOX® 47.1% vs. placebo 35.1%; $P < .001$).[6] At completion of the 56-week open-label treatment phase of PREEMPT, 68.8% of the further treated BOTOX® group had at least a 50% decrease from baseline in the frequency of headache days.[7] There was very little discussion on this topic and its implications for patient care decisions at the July 11, 2014 CTAF meeting. This is an important component in any transparent discussion considering the "value" of BOTOX® treatment. We request that this real-world perspective from your panel of headache experts, which is supported by PREEMPT study results, be included in the final CTAF report as evidence supporting the high value of BOTOX® treatment.

During the July 11, 2014 meeting, CTAF/ICER presented as "benchmarks" the results from a cost-effectiveness study of oral migraine prophylactics.[8] The sources for these data were not identified in the presentation on July 11, 2014 nor were they mentioned in the draft report. In addition, these data were incompletely presented without any information on the quality and appropriateness of the underlying effectiveness data and economic model. The presented results compared active treatments vs. oral placebo (not sham injection) and reported that the cost per headache day averted was as follows: Topiramate = $115, Divalproex = $48, Gabapentin = $138.

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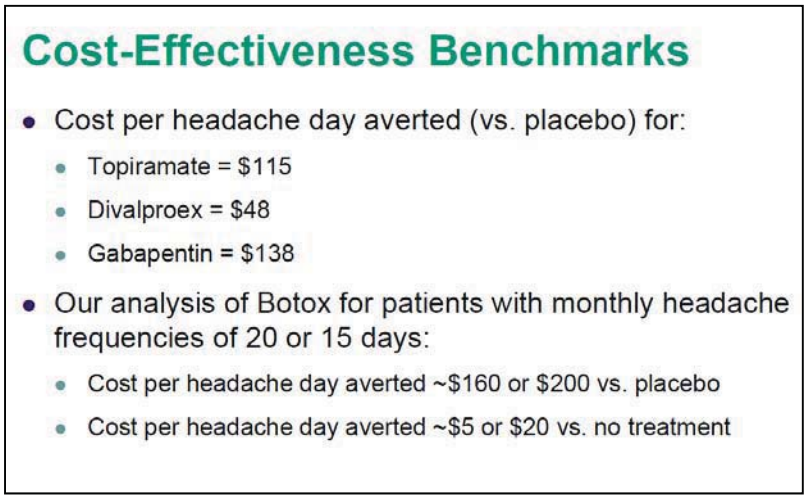
[6] Dodick DW, Turkel CC, DeGryse RE, *et al*. PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010;50(6): 921–936.

[7] Aurora SK, Winner P, Freeman MC, *et al*. OnabotulinumtoxinA for treatment of chronic migraine: Pooled analyses of the 56-week PREEMPT clinical program. Headache 2011;51: 1365-1367.

[8] See Slide 51 of the CTAF presentation slides.



It is unclear based on the minimal information presented about this data, how the CTAF panel could objectively consider these data elements to inform their interpretation of the CTAF model results, and their subsequent vote to Question 3a. Regardless, it would appear that these data elements would support a determination of high value considering the effectiveness of BOTOX® in chronic migraine and the cost per headache averted vs. no treatment. We identified what we believe are the published literature for these data elements, and found fundamental limitations of the results that create relevant uncertainties for its interpretation. We request that these be transparently presented, and accordingly adjusted for in the final CTAF report:

- The costs in the model appear to be reported in 2002 dollars. A reasonable, customary, and generally accepted methodological consideration when presenting this data as a benchmark for use in a value determination would be to update the costs to 2014 dollars, allowing a less-biased and "apples to apples" comparison with the results of the CTAF economic model. Using the Bureau of Labor Statistics consumer price index calculator (http://data.bls.gov/cgi-bin/cpicalc.pl accessed July 21, 2014 at 3:30PM PST) these values, inflated to 2014 dollar, are $152.08 for topiramate, $63.48 for divalproex, and $182.49 for gabapentin.
- The benchmark results are versus an oral placebo, which is different from the PREEMPT placebo (which was not an oral placebo) and consisted of 31 intramuscular injections of saline per the PREEMPT injection paradigm.
- The benchmark results were from a population of patients with episodic migraine, which as presented in our July 2, 2014 communication and supported by headache specialists at the July 11, 2014 CTAF meeting is a separate disorder from chronic migraine. Therefore, given the more debilitating nature of chronic migraine compared to episodic migraine, one cannot assume that the dollar per headache day averted for a chronic migraine patient is comparable to that for a patient with episodic migraine.

Economic Model Corrections and Updates.

As communicated in our July 2, 2014 letter, we replicated the economic model described in the draft CTAF report and found several fundamental and serious errors. It is our understanding, based on the handout provided at the meeting on July 11, 2014 that some of these errors have been corrected, including:

(1) Over estimation of BOTOX® costs by 81%

(2) The erroneous inclusion of "Placebo" effectiveness for the "No Therapy" comparator group
(3) The inclusion of patients with episodic migraine (i.e., <15 headache days per month)
(4) The inappropriate comparison with amitriptyline, which is neither indicated for chronic migraine nor does it have any head-to-head clinical trial evidence with BOTOX®

While the revised CTAF model corrected the erroneous inclusion of placebo effectiveness for the "No Therapy" group and the other points above, it appears that the CTAF model results presented at the July 11, 2014 meeting continued to fail to account for a cost that would be associated with the sham injection (which is the same 31 injection-site procedure for BOTOX® treatment) for the PREEMPT placebo comparison. We previously noted this omission to the cost assumptions for the CTAF model in our July 2, 2014 letter, and again request for the CTAF model and final report to be corrected to account for this. The exclusion of a cost for the sham injection (PREEMPT placebo) creates a non-transparent and non-evidence-based bias in the cost-effectiveness ratio in favor of placebo because the model accounts for the observed benefit of placebo (sham-injection) from PREEMPT, but not a cost that would be associated with the time, materials, and skill for an injector to provide the 31 intramuscular saline injections. In addition, the CTAF model incorrectly assumes that placebo (sham injection) cohort patients will be 100% persistent; however, the clinical trial evidence from PREEMPT and the systematic literature review by Hepp et al. (2014) clearly show that patients discontinue placebo in chronic migraine and other migraine diagnoses due to a variety of reasons and therefore is a relevant model input to parameterize. We request that CTAF revise the model and final report to include a cost for the PREEMPT placebo (sham injection) and a parameter estimate for placebo persistency rate to ensure completeness and transparency, and to minimize any unintended bias favoring the placebo cohort.

Model Summary and Sensitivity Analyses for CTAF Final Report.

Table 2 below, summarizes the results of the draft model, presenting first the results in the original CTAF draft report without correction of errors, the results of the CTAF model presented at the July 11, 2014 meeting, and the additional model revisions/analyses Allergan requests be included in the final report for the points outlined above. It also includes a sensitivity analysis to appropriately capture data on all-cause discontinuation for BOTOX® treatment and placebo (sham injection) from PREEMPT.

Table 2. Cost per Headache (HA) Day Averted for BOTOX® Treatment vs. Comparator, by Baseline HA Days

Model Variation	**Vs. No Treatment**		**Vs. Placebo**	
	20 HA Days	15 HA Days	20 HA Days	15 HA Days
CTAF Model Presented in Original Draft Document	$147.25	$255.77	$286.97	$396.07
CTAF Model Presented at July 11, 2014 Meeting (Correcting for true BOTOX® cost and fixing the error in the number of headache days with no treatment)	$3.99	$18.93	$157.36	$223.26

Correction with cost for sham-injection for PREEMPT placebo (Assuming a cost of $104 per sham injection)	$3.99	$18.93	$139.68	$199.85
Sensitivity Analysis: Overall Persistence (Adjusting persistence rates to include all-cause discontinuation for both BOTOX® and placebo)	$5.03	$20.33	$135.63	$194.45

The results demonstrate that BOTOX® treatment not only provides a net health benefit (as agreed on by a unanimous vote "yes" by the CTAF panel members) but also provides this benefit at a very reasonable cost per headache days averted.

Request for Final Report.

We request CTAF not publish the report until all of the model issues and recommendations described above have been addressed, all appropriate tables and figures updated with the new model results and integrated into the report, and the amitriptyline model scenario removed from the entire Section 7.4 as it is not an appropriate analysis based on: (1) the use of a different biologic, abotulinumtoxinA (DYSPORT®) rather than onabotulinumtoxinA (BOTOX®) in the cited study and (2) the lack of evidence supporting the use of amitriptyline in adult patients with chronic migraine. We include our updated Excel-based replication of the CTAF/ICER model for reference.

Question 4: For patients who are considering multiple therapeutic options for chronic migraine, is the evidence adequate to demonstrate that the net health benefits of BOTOX® injections used on an every 12-week schedule are equivalent to or better than those of other preventive therapies?

Summary response: The evidence regarding the safety and efficacy of oral migraine preventive medications is not sufficiently developed, either with respect to their use in patients with chronic migraine nor in comparison to treatment with onabotulinumtoxinA (BOTOX®) to allow for the assessment of whether the net health benefit of BOTOX®, when administered for the prophylaxis of headaches in chronic migraine and consistent with the product's instructions for use, is equivalent or better than those of other preventive therapies. The literature does not support a conclusion that the oral migraine preventive medications are effective and safe for the treatment of chronic migraine and therefore does not allow for a comparative assessment of the value of BOTOX®. The draft report, upon which the panel voted, did not include an evidence-based analysis of these oral migraine prevention medications. We strongly recommend that question 4 and any associated voting be removed from the "Controversies in Migraine Management" technology assessment until a comprehensive therapy review of the oral migraine preventive medications is completed and added to the final report.

Detailed response: In addition to the concerns previously highlighted within Allergan's response submitted on July 2, 2014, the information provided below addresses concerns expressed during the July 11, 2014 public meeting and contained within CTAF's draft report. The evidence supporting the use of oral medications in the prevention of chronic migraine is limited and does not support a conclusion that

the oral migraine preventive medications are effective and safe for the treatment of chronic migraine, and therefore does not allow for a comparative assessment of the value of BOTOX®.

For example, on page 5 of the draft report, the statements, "Many classes of medications are effective at reducing the frequency and intensity of migraine headaches. These include beta-blockers (propranolol, metoprolol), anti-convulsants (valproate, topiramate), anti-depressants (amitriptyline, venlafaxine), angiotensin converting enzyme inhibitors (lisinopril), calcium channel blockers (nicardipine), and angiotensin receptor blockers (candesartan)" are misleading. Only three drugs in two of these classes have published randomized trials specifically for chronic migraine – amitriptyline in the anti-depressant class and topiramate and valproate in the anti-convulsant class. The rest have been studied primarily for episodic migraine. The final report should acknowledge this fact or remove the statement.

Publications Detailing the Randomized, Placebo-Controlled Trials that Support the Use of the Oral Products in the Treatment of Chronic Migraine Are Subject to Significant Limitations.

The draft report, upon which the panel voted, did not include an evidence-based analysis of these oral migraine prevention medications. The literature is limited in terms of studies conducted with oral medications for migraine prevention vs. placebo controlled trials. To identify some of the concerns with randomized controlled trials of oral migraine preventive vs. placebo controls in a chronic migraine population, a literature search of drugs for the prophylactic treatment of chronic migraine was conducted by Allergan's Global Information and Literature Services on November 19, 2013. Databases searched were STN International files, Medline, and Biosis. The search strategy included classes of and/or specific drugs that have been studied for use in the prophylactic treatment of chronic migraine. The following drugs and terms were identified for the search: antiepileptic(s)s, anticonvulsant(s), beta blocker(s), ACE inhibitor(s), antidepressant(s), angiotensin receptor blocker(s), alpha agonist(s), antihistamine(s), divalproex sodium, sodium valproate, topiramate, metoprolol, timolol, propranolol, amitriptyline, venlafaxine, lisinopril, candesartan, clonidine, guanfacine, cyproheptadine AND chronic migraine, chronic daily headache, prophylactic, --comprehensive, --last 10 years, --English only, --include reviews and non-peer-reviewed literature. The following types and numbers of studies were identified: Clinical Studies, Case Reports, Systematic Reviews and Meta-Analyses (3); General Reviews (156); Appendix: Search details (250).

Summarized below are selected articles from this search, primarily consisting of randomized, controlled trials[9] using anticonvulsants or antidepressants (although not limited to these classes) which often are cited in the literature in the treatment of chronic migraine and drugs identified in AAN's Evidence-based Guidelines Update, Pharmacologic Treatment for Episodic Migraine in Adults that were studied for use in chronic daily headache/chronic migraine/chronic tension type headaches with the results separated out by more than one headache type. Additionally, tizanidine was specifically reviewed due to interest expressed by a CTAF panel member:

- In Diener et al.'s 2007 European Topiramate in Chronic Migraine (TOPCHROME) study (n=59), 32 patients received topiramate (mean dose, 100 mg/day) and 27 patients received a placebo.[10]

[9] Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78: 1337-1345.

[10] Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ;TOPMAT-MIG-201(TOP-CHROME) Study Group. Topiramate reduces headache days in chronic migraine: A randomized, double-blind, placebo-controlled study. Cephalalgia. 2007;27(7):814–823.

Concomitant antidepressant use was allowed if the dose was stable at least 3 months prior to trial entry and the patients intended to take it throughout the trial. Use of other anticonvulsants was not allowed. The authors reported that topiramate significantly reduced the mean number of monthly migraine days by 3.5 compared with the placebo, and 22% of chronic migraine patients had a 50% or greater reduction in the mean number of headache days per month. Health related quality of life improvement was found in MIDAS,[11] but no change in HIT-6[12] or MSQ[13] was found. Tolerability was assessed by adverse event reports and early trial discontinuation. The discontinuation rate was 25% (topiramate) vs. 48% (placebo). Treatment emergent adverse events were reported by 75% of topiramate-treated patients and by 37% of placebo-treated patients). The most common AEs, paraesthesia (53% vs. 7%), nausea (9% vs. 0%), dizziness (6% vs.0%), dyspepsia (6% vs.0%), fatigue (6% vs. 0%), anorexia (6% vs. 4%) and disturbance in attention (6% vs. 4%) of topiramate-treated patients vs. placebo-treated patients. With small numbers overall and only 24 out of 32 topiramate patients and 14 out of 27 placebo subjects completing the study, it is difficult to generalize the study results.

- Silberstein et al.'s 2007 16-week, randomized, placebo-controlled, parallel-group, multicenter trial conducted in the U.S. evaluated the efficacy of topiramate in the treatment of chronic migraine.[14] The intent-to-treat population included 306 (topiramate, n = 153; placebo, n = 153) of 328 randomized subjects who provided at least one efficacy assessment. Chronic migraine patients experienced significant reductions in the mean monthly number of migraine/migrainous days (1.7 days) and the mean number of migraine days following therapy with topiramate vs. placebo (1.5 days) compared to baseline. Discontinuations due to adverse events were 10.9% for topiramate and 6.1% for placebo groups. Treatment-related adverse events occurred in 82.5% of topiramate-treated patients (vs. 70.2% in the placebo treated group). The most commonly reported treatment-related adverse events in the topiramate group (vs. placebo) were paresthesia (28.8% (vs. 7.5%)), fatigue (10.6% (vs. 9.3%)), difficulty with concentration (9.4% (vs. 2.5%)), dry mouth (6.2% (vs. 2.5%)), and nausea (6.2% (vs. 6.3%)).Discontinuations due to adverse events occurred in 18 (10.9%) topiramate subjects and 10 (6.1%) placebo subjects. There were no serious side effects or deaths.

- Couch et al., representing the Amitriptyline Versus Placebo Study Group, published a reanalysis of a double-blind, placebo-controlled trial (n=391) based on data collected between 1976-1979 in patients with migraine or chronic daily headache.[15] Results of the sub-group analysis in 58 patients (amitriptyline n=36, placebo n=22) with chronic daily headache (>17days per month concluded amitriptyline titrated to 100 mg daily was "statistically significantly superior to placebo in the number of patients with improvement in frequency > 50% at 8 weeks and 16 weeks with a similar but non-significant trend at 12 and 20 weeks. Of the 58 chronic daily headache patients enrolled at week 8, only 32 remained by week 20, a nearly 45% discontinuation

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[11] Migraine Disability Assessment.

[12] Headache Impact Test.

[13] Migraine Specific Quality of Life Questionnaire, Version 2.1.

[14] Silberstein SD, Lipton RB, Dodick DW, Freitag FG, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: A randomized, double-blind, placebo-controlled trial. Headache 2007;47:170-180.

[15] Couch JR, Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache. 2011;51(1):33–51.

rate. Discontinuation and adverse event rates were not separately reported for patients with chronic daily headache. In the study population as a whole, however, 48% (93/194) of amitriptyline and 54% (106/197) of placebo patients discontinued the study before 20 weeks. The major individual adverse events for which there were significant differences in occurrence between groups included dry mucous membranes, constipation, urinary retention, dizziness, and somnolence. This study was analyzed as a "Completer "study and not as an "Intent to Treat" (ITT) since an ITT approach for analysis of clinical trials was not in common use in 1976. There was no standard definition of migraine at the time the study was initiated. Therefore, it is difficult to assess the relationship of the results in patients identified with migraine to chronic migraine. The small number of patients included in the Completer analysis given the discontinuation rate (45%) precludes generalizing the study results.

- A previous search identified three articles with amitriptyline for migraine prophylaxis published in 1973, 1979, and 1987. An analysis of these articles is provided due to amitriptyline's Level B rating for the prevention of episodic migraine by AAN. Due to limiting our review to studies of patients with chronic migraine or chronic daily headache, these studies of amitriptyline should not be included for comparative purposes.

    - Gomersall and Stuart: Amitriptyline in migraine prophylaxis.[16] Changes in pattern of attacks during a controlled clinical trial. Of 26 volunteers, 20 completed the trial; the only definition for inclusion was more than 2 headaches per month and 50% of these headaches were of at least moderate severity.

    - Couch and Hassanein: Amitriptyline in Migraine Prophylaxis.[17] Only inclusion criteria was 2 disabling or severe migraine headaches in the month prior to induction the study. Amitriptyline (n=47) and placebo (n=53).

    - Ziegler et al. (1987): Amitriptyline and Propranolol in Migraine Prophylaxis.[18] Double blind, placebo controlled crossover design. Not conducted in a chronic migraine or a chronic daily headache, n=54 and 30 participants completed the study. Patients must have had headaches that occurred not less than an average of twice a month nor more often than 3 times a week. Both drugs were found to be superior to placebo.

      Due to limiting our review to studies of patients with chronic migraine or chronic daily headache, these studies of amitriptyline should not be included for comparative purposes.

- Yurekli et al: The efficacy of sodium valproate (VPA) was evaluated in a small group of 29 chronic migraine patients and 41 chronic tension-type headache patients.[19] Patients were

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[16] Gomersall and Stuart (1973):Amitriptyline in migraine prophyaxis. Changes in pattern of attacks during a controlled clinical trial. Journal of Neurology, Neurosurgery, and Psychiatry, 1973, 36, 684-690.

[17] Couch JR, Hassanein R. Amitriptyline in Migraine Prophylaxis. Arch Neurol 1979;36:695-699.

[18] Ziegler DZ, Hurwitz A. Hassanein, RS. Migraine Prophylaxis. A Comparison of Propranolol and Amitriptyline. Arch Neurol 1987;44:486-489.

[19] Yurekli VA, Akhan G, Kutluhan S, Uzar E, Koyuncuoglu HR, Gultekin F. The effect of sodium valproate on chronic daily headache and its subgroups. J Headache Pain. 2008;9(1):37–41.

randomized to 500 mg twice a day or placebo for 3 months, and a significant improvement in the severity and frequency of pain was reported in the CM subgroup. The objective of the study was to assess the efficacy and tolerability of sodium valproate (VPA) on chronic daily headache in a prospective, double blind, randomized, placebo-controlled trial. Seventy patients were included in the study. Only 29 had chronic migraine, while 41 had chronic tension-type headache. Given the small size of the study – 29 patients in the chronic migraine group, specifically 17 VPA and 12 placebo – and the use of a Visual Analog Scale as the primary endpoint, this study should not be considered of sufficient quality to support a comparative assessment versus BOTOX®.

- Saper et al.: The randomized, placebo controlled multi-center study (n=200) of tizanidine vs. placebo as adjunctive prophylactic therapy of chronic daily headache (chronic migraine, migrainous headache, or tension-type headache) included patients who could stay on other concurrent preventative medications except those with alpha-adrenergic properties.[20] 92 patients completed at least 8 weeks of treatment and 95 patients met criterion for efficacy analysis. Primary outcome was the Headache Index from patient diaries. Results reported were for all HA types (migraine+ migrainous+ TTH), no subgroup analysis was performed for CM. At week 12 tizanidine was superior to placebo in reducing overall headache index (p=.025) vs. placebo. Although authors combined the tizanidine-treated migraine and migrainous patients into a group and compared to the TTH for efficacy, this was a post hoc analysis and the authors did not report any specific variances – only that there was no difference between the 2 groups. Since no results were reported for CDH-migraine population, one would not include this study in a review of evidence for oral medications for chronic migraine prevention. The AAN's evidence-based guidelines for episodic migraine pharmacological treatment did not provide any recommendations regarding tizanidine in its guideline.[21]

- A June 2014 publication by Stovner et al., "A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomized, triple-blind, placebo-controlled, double cross-over study" in which investigators sought to determine if the effect of candesartan for migraine prevention reported previously could be shown to be effective in a migraine population.[22] Of the 72 episodic and chronic patients included, only 1 patient was listed as having chronic migraine which prohibits its use for analysis in a chronic migraine population for effectiveness.

No Oral Product is FDA-Approved for the Treatment of Chronic Migraine.

Amitriptyline is not FDA-approved for the prophylaxis of any type of headache, including chronic migraine. Topiramate is FDA-approved for the prophylaxis of migraine headache, but not specifically for chronic migraine. The Level A and Level B evidence of anticonvulsants and antidepressants used in

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[20] Saper JR, Lake AE, Cantrell DT, Winner PK, White JR. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study.

[21] Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78:1337-1345.

[22] Stovner LJ, Linde M, Gravdahl GB. et al, "A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomized, triple-blind, placebo-controlled, double cross-over study. Cephalalgia 2014;34(7)523-532.

prophylactic migraine treatment have been in the episodic migraine populations, not in chronic migraine patients (refer to AAN Practice Parameters for Episodic Migraine).[23] As data with BOTOX® itself has shown, one cannot extrapolate data in patients with episodic migraine to infer the effectiveness or safety of a product in chronic migraine.

The CTAF draft report also commented on the 2012 published meta-analysis by Jackson et al., "Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: a meta-analysis."[24] Specifically, the conclusions cited in CTAF's draft report were "This systematic review and meta-analysis found that botulinum toxin is not effective for the prevention of episodic migraines (9 studies, 1,838 participants) but is more effective than sham injections for chronic migraines (5 studies, 1,508 participants). In head-to-head trials, botulinum toxin was not associated with a reduction in headache frequency compared with topiramate, amitriptyline, or valproate."

Comparative Data Against BOTOX® is Insufficient.

The three small, randomized head-to-head trials in patients with chronic migraines that were direct comparisons of botulinum toxin to preventive therapies for episodic migraines (topiramate,[25] amitriptyline[26]) had too small a sample size (n = 59, 60, and 79) to demonstrate equivalence or superiority. The amitriptyline study that used DYSPORT® as the comparator, which is a different biological from BOTOX®, should not be included in the final report as the evidence for the safety and efficacy of BOTOX® cannot be extrapolated to DYSPORT®. The evidence supporting the use of topiramate or amitrypyline in the prophylaxis of headaches in patients with chronic migraine is limited.

As noted by CTAF, the majority (ten) of the studies included in Jackson's meta-analyses involved patients with episodic migraine.[27] The Jackson report did include seven studies in patients with chronic migraine and three studies in patients with chronic daily headache. Among the seven studies in CM, the Magalhaes et al. study involved treatment with a different biological – abobotulinumtoxinA (DYSPORT®) (BOTOX® is onabotulinumtoxinA).[28] Most trials allowed continued use of prophylactic headache medications (85%), if patients were taking a stable dose, and all allowed analgesic use. Different injection protocols were followed for administration of BOTOX®. The authors stated major

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[23] Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78: 1337-1345.

[24] Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: A meta-analysis. JAMA 2012;307(16):1736-1745.

[25] Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX®) and topiramate (TOPAMAX®) for the prophylactic treatment of chronic migraine: a pilot study. Headache 2009;49(10):1466-1478; Cady RK, Schreiber CP, Porter JA, Blumenfeld AM, Farmer KU. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache. Jan 2011;51(1):21-32.

[26] Magalhaes E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clinical Neurology and Neurosurgery. Jul 2010;112(6):463-466.

[27] Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: A meta-analysis. JAMA 2012;307(16):1736-1745.

[28] Magalhaes E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clinical Neurology and Neurosurgery. Jul 2010;112(6):463-466.(REF 76 in CTAF report).

limitations as "1) relatively few studies and many of the studies were quite small. Our results could be spurious…; 2) we only had aggregate data. Many of the outcomes had considerable heterogeneity and the lack of patient-level data preclude fully exploring potential sources of differences between studies; 3) headache is a chronic problem and all trials were relatively short… prophylactic treatment can be more effective over time; 4) none of the studies evaluated more than 3 injections, 90 days apart. It is unclear if higher dosing over time may be associated with greater benefit; 5) there are few comparison between botulinum toxin A and other prophylactic medications, and these are underpowered or have limitations that may prevent the ability to demonstrate benefit of botulinum toxin A."

Jackson's meta-analysis did conclude that botulinum toxin A may be associated with benefit in prophylaxis of chronic daily headaches and chronic migraine headaches.[29] The headache-related burden and disability in chronic migraine patients is multi-faceted, encompassing headache frequency, duration, and severity. The need for evaluating multiple outcomes in treating chronic migraine patients instead of just a single primary endpoint where success or failure of the patient is determine by a single variable is critical.

Oral Migraine Prophylactics Have Poor Adherence and Persistence Rates.

The headache-related burden and disability in chronic migraine patients is multi-faceted, encompassing headache frequency, duration, and severity.[30] Mathew et al. states "Thus, while there is need for effective preventative treatment in the chronic migraine population, migraine prevention with oral daily medications presents a number of challenges affecting patient adherence and compliance with drug regimens, including daily dosing regimens and frequency of required follow-up."[31]

Blumenfeld et al.'s 2013 article" Patterns of Use and Reasons for Discontinuation of Prophylactic Medications for Episodic Migraine and Chronic Migraine: Results From the Second International Burden of Migraine Study (IBMS-II)" characterized patterns of preventive medication use in persons with episodic migraine and chronic migraine from data collected in an international, web-based, cross-sectional survey of adults with migraine during 2010.[32] Of 1165 respondents who completed the survey, less than half (28.3% of episodic migraine and 44.8% chronic migraine) of respondents were currently using preventive medication.

Many chronic migraine patients may fail to take preventive medication. Observational studies and pooled data from randomized trials have demonstrated poor adherence to migraine prophylaxis. A systematic literature review, published by Hepp et al. earlier this year, summarized published observational and randomized controlled studies on the adherence and persistence to the three most commonly prescribed

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[29] Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: A meta-analysis. JAMA 2012;307(16):1736-1745.

[30] Dodick DW, Turkel CC, DeGryse RE, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: Pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 2010;50:921-936.

[31] Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache. 2009;49(10):1466–1478.

[32] Blumenfeld AM, Bloudek LM, Becker WJ, Buse, DC; Varon SF*, Maglinte GA, Wilcox TK, Kawata AK, Lipton RB. Patterns of Use and Reasons for Discontinuation of Prophylactic Medications for Episodic Migraine and Chronic Migraine: Results From the Second International Burden of Migraine Study (IBMS-II) Headache 2013;53:644-655. Varon is an Allergan employee as was Bloudek at time when article was written; Bloudek is now a former Allergan employee.

oral migraine prophylactic medications (topiramate, propranolol, and amitriptyline).[33] A total of 788 unique articles were identified using the search criteria, 33 of which were included in the final review. Observational studies (n = 14) showed adherence ranges of 41% to 95% at 2 months, 21% to 80% at 6 months, and 35% to 56% at 12 months and persistence ranges of 41% to 88% at 2 months, 19% to 79% at 6 months, and 7% to 55% at 12 months. Pooled persistence from RCTs on propranolol, amitriptyline, and topiramate (n = 19) showed rates of 77%, 55%, and 57%, respectively, at 16-26 weeks. Adverse events were the most common reason for discontinuation cited (24% for topiramate and 17% for amitriptyline).

Discontinuation	Topiramate	Amitriptyline	Propranolol	Placebo
Rates by Cause	(%)	(%)	(%)	(%)
Adverse events	23.70	16.74	7.77	6.96
Patient choice	5.56	18.56	1.21	6.25
Lost to follow-up	3.43	6.30	2.95	3.77
Other	8.45	9.53	6.97	15.45

Ref: Hepp Z*, Bloudek* LM, Varon SF*. Systematic review of migraine prophylaxis adherence and persistence. JMCP 2014;20:(1)22-33.[34]

BOTOX® is Well Tolerated.

Safety results in addition to efficacy should be considered, especially in light of study sample size. The PREEMPT studies included the largest number of subjects ever studied for chronic migraine in a randomized placebo controlled trial (n=1384). In the PREEMPT Pooled, Double-Blind (DB), Placebo-Controlled Trial[35] a total of 62.4% (BOTOX®) and 51.7% of patients (placebo) reported an adverse event in the DB phase, with 29.4% (BOTOX®) vs. 12.7% (placebo) being treatment-related.[36] Most patients reported adverse events that were mild to moderate in severity and few discontinued (BOTOX® 3.8% vs. placebo 1.2%) due to adverse events. No unexpected treatment-related adverse events were identified.

In the 56-Week PREEMPT Clinical Program: Open Label Phase most patients (72.6%) completed the open-label phase; 58.3% of patients reported an adverse event with 20.3% of patients reporting a treatment-related adverse event.[37] Few (only 4.6%) discontinued due to adverse events. No new safety or tolerability issues emerged.

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[33] Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. JMCP 2014;20:(1)22-33. Hepp and Varon are Allergan employees as was Bloudek at time when article was written; Bloudek is now a former Allergan employee.

[34] Hepp and Varon are Allergan employees as was Bloudek at time when article was written, Bloudek is now a former Allergan employee.

[35] AE data for this section is taken from Tables 3 and 4 of the Aurora 56-wk PREEMPT clinical program; pg 1368 for tables.

[36] Dodick DW, Turkel CC, DeGryse R, et al; PREEMPT Chronic Migraine Study Group. OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache. 2010;50(6): 921–936.

[37] Aurora SK, Winner P, Freeman MC,et al. OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Analyses of the 56-Week PREEMPT Clinical Program Headache. 2011 Headache 2011;51:1358-1373

The proportion of patients who experienced a serious adverse event during the double-blind (DB) phase (BOTOX® 4.8 %; placebo 2.3%) or Open Label (OL) phase (3.8%) was low.[38] Treatment-related serious adverse events were experienced by one (0.1%) patient each in both the DB and OL Phases. The incidence rates for individual treatment-related AEs were consistent with the known pharmacology and established safety of BOTOX® when injected into head and neck muscles. The only individual treatment-related AEs occurring at a rate of more than 5% during the DB phase were neck pain in the BOTOX® group (6.7%) and muscular weakness (5.5%). In the OL phase, when all patients were exposed to BOTOX®, there were no individual treatment-related AEs occurring at a rate exceeding 5%. The majority of all reports of neck pain, the most commonly reported AE in both the DB and OL phases was rated as mild or moderate in severity and none were reported as serious AEs. Neck pain did not occur consistently with repeated BOTOX® treatment, as incidence rates declined with subsequent treatment cycles. Over the entire 56-week PREEMPT clinical program, the overall adverse event rate progressively decreased with subsequent BOTOX® treatments, indicating that sustained treatments with injections of 155 to 195 U of BOTOX® every 12 weeks were safe and well tolerated.

PREEMPT Data Results Affirm That the Adverse Effect Profile for BOTOX® is Less than What was Cited in the CTAF Draft Assessment. BOTOX® Was Well Tolerated in the PREEMPT Trials.

Table 5 of the draft report identifies muscle weakness, neck pain, neck stiffness, drooping eyelid and paresthesia as adverse events observed in randomized trials of botulinum toxin for the prevention of migraine headaches that were likely associated with active treatment. However, with the exception of paresthesia, the rates of adverse events shown in Table 5 in the CTAF draft report are substantially larger than the adverse event rates reported in the double-blind and open-label phases of the PREEMPT trials, respectively:

Adverse event	Rate Reported in Draft Assessment (vs. placebo) (n=variable depending on indication and treatment arm)	Rate Reported During Double-Blind Phase of PREEMPT Trials (vs. placebo) (n=687 BOTOX®; 692 placebo)	Rate Reported During 32-Week Open-Label Phase of PREEMPT Trials (n=1,205)
Any adverse event	57% (vs. 46%)	29.4% (vs. 12.7%)	20.3%
Muscle weakness	21% (vs. 2%)	5.5% (vs. 0.3%)	3.9%
Neck pain	19% (vs. 4%)	6.7% (vs. 2.2%)	4.6%
Neck stiffness	14% (vs. 4%)	2.3% (vs. 0.7%)*	1.7%
Drooping eyelid	8% (vs. 1%)	3.3% (vs. 0.3%)	2.5%
Parasthesia	3% (vs. 1%)	3.2% (vs. 2.0%)**	2.0%

*Figures represent reports of "musculoskeletal stiffness" during PREEMPT trials
**Figures represent reports of "injection-site pain" during PREEMPT trials

The rates reported in the draft assessment appear to be derived from a 2012 meta-analysis. Assuming this is the source of the event rates, it is important to note that in calculating the above-referenced figures, the

[38] Tables 3 and 4 reproduced from Aurora SK, Winner P, Freeman MC,et al. OnabotulinumtoxinA for Treatment of Chronic Migraine: Pooled Analyses of the 56-Week PREEMPT Clinical Program Headache. 2011 Headache 2011;51:1358-1373.

authors of the meta-analysis included adverse event reports from studies in patients (a) diagnosed with a type of headache other than chronic migraine (i.e., episodic migraine, chronic daily headache, or chronic tension-type headache) and (b) administered BOTOX® in a manner that is not consistent with the injection paradigm set forth in the BOTOX® package insert.[39] Results from studies in patients with headache disorders other than chronic migraine and/or which do not employ the PREEMPT dosage and injection paradigm cannot be used to assess the current safety and efficacy of BOTOX® for the treatment of chronic migraine.

The safety of oral migraine preventive medications should also be addressed in CTAF's draft report as Table 5 only highlights the safety of BOTOX® but not the oral agents against which BOTOX® is being compared. As noted on Page 5 of the draft report, "The medication choice is usually based on an indication for a particular drug class because of concomitant conditions and tolerability." The CTAF draft report notes that "We chose amitriptyline as an additional comparator given its milder side-effect profile in comparison to the anticonvulsants." This reference is to the Magalhaes study that used DYSPORT® rather than BOTOX® as the comparator to amitriptyline.[40] The known adverse effect profile the anticonvulsants influenced the choice of the oral medication selected for study.

Intent of Revised Question.

Finally, we direct our clinical response to address the intent of the revised question: "For patients who are considering multiple therapeutic options for chronic migraine, is the evidence adequate to demonstrate that the net health benefits of BOTOX® injections used on an every 12-week schedule are equivalent to or better than those of other preventive therapies?"

We respectfully request that you review the discussion conducted by the moderator and the voting panel immediately prior to the question 4 vote. (Unedited webinar recording; time stamp: 3:48:58 – 3:54:00). This discussion infers that by voting "yes", the panel would be endorsing BOTOX® as first line treatment in chronic migraine.[41] Insofar as the voting question was inquiring about the equivalence of BOTOX® to other therapies (which, as noted above, we believe the evidence is not sufficient to assess), we respectfully assert that a positive vote would not have implied that BOTOX® should be used as first line therapy as the question was addressing the adequacy of the comparative evidence.

There is sufficient evidence to show that BOTOX® is effective and safe in the management of chronic migraine. There are limited data with other products—some products have no data in chronic migraine—and even less that is comparative. Therefore, CTAF cannot make the comparison suggested by Q4. This should not be taken to mean that BOTOX® is of low value—it is more a reflection of the lack of evidence (data) on other products (vs. placebo or no therapy) in the chronic migraine population as well as the lack of comparative data vs. BOTOX®.

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[39] Jackson JL, Kuriyama A, Hayashino Y. Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults: A meta-analysis. JAMA 2012;307(16):1736-1745.

[40] Magalhaes E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clinical Neurology and Neurosurgery. Jul 2010;112(6):463-466.

[41] CTAF's unedited webinar recording. Time stamp: 3:48:58 – 3:54:00, accessed 7/21/2014 at: http://ctaf.org/reports/controversies-migraine-management.

In addition to comments Allergan previously provided both orally and in writing, we respectfully request that the following changes be made to the draft report, before final publication:

1. Page 5: The CTAF report references Shamliyan TA, Choi JY, Ramakrishnan R, et al. Preventive pharmacologic treatments for episodic migraine in adults.[42] As the article addresses episodic and not chronic migraine, it should either be omitted or, if retained for the final report, accompanied by an explanation regarding its inclusion.

2. Page 5: The CTAF report states "Many classes of medications are effective at reducing the frequency and intensity of migraine headaches. These include beta-blockers (propranolol, metoprolol), anti-convulsants (valproate, topiramate), anti-depressants (amitriptyline, venlafaxine), angiotensin converting enzyme inhibitors (lisinopril), calcium channel blockers (nicardipine), and angiotensin receptor blockers (candesartan)." Only 3 drugs in 2 of these classes have published randomized trials specifically for chronic migraine: amitriptyline (antidepressants), and topiramate and valproate (anticonvulants). The rest have been studied primarily for episodic migraine. The CTAF report should acknowledge that conclusions about the effectiveness of other medicines as preventive therapies in patients with chronic migraine cannot be made due to lack of evidence.

3. Page 16, Section 4.2: The systematic review section includes the article by Shuhendler AJ, Lee S, Siu M, et al. "Efficacy of botulinum toxin type A for the prophylaxis of episodic migraine headaches: a meta-analysis of randomized, double-blind, placebo-controlled trials. Pharmacotherapy. Jul 2009;29(7):784-791".[43] As this review article only addresses episodic migraine, we ask that it be deleted. CTAF's statement that "This systematic review and meta-analysis of 8 randomized trials with 1,601 participants concluded that Botulinum toxin A for the preventive treatment of episodic migraine headaches was not significantly different from placebo, both statistically and clinically." This systematic review centers on only episodic migraine and did not include chronic migraine, and thus is not relevant for BOTOX® and should not be included in the final report.

4. Page 27: Remove Chankrachang's study using from the evidence table, as it was conducted using DYSPORT® and not BOTOX®.

5. Page 28, Table 5: Adjust the adverse event rates to reflect PREEMPT trial data.

6. Page 29, End of Second Paragraph: A full discussion of quality of life data is required here. Statistically significant reductions in the proportions of patients with severe HIT-6 scores and significant improvement in the MSQ questionnaire results were noted in PREEMPT in addition to the results already listed in the draft document.

7. Page 30, Paragraph 5: While technically correct that "There are three small, randomized trials in patients with chronic migraines that directly compare botulinum toxin to established preventive therapies for episodic migraines (topiramate, amitriptyline)," the report should acknowledge that

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[42] Shamliyan TA, Choi JY, Ramakrishnan R, et al. Preventive pharmacologic treatments for episodic migraine in adults. Journal of General Internal Medicine. Sep 2013;28(9):1225-1237.

[43] Shuhendler AJ, Lee S, Siu M, et al. Efficacy of botulinum toxin type A for the prophylaxis of episodic migraine headaches: a meta-analysis of randomized, double-blind, placebo-controlled trials. Pharmacotherapy. Jul 2009;29(7):784-791.

the amitriptyline study used a different botulinum toxin (DYSPORT®) vs. BOTOX® and that the data cannot be extrapolated from one botulinum toxin to another.

8. Page 30, Paragraph 5: The statement that "there was a trend towards greater headache prevention with the oral therapies" based upon two poorly designed and underpowered studies comparing BOTOX® to topiramate is incorrect. Only the Cady study showed oral treatment to have a trend towards better response while Mathew et al. showed BOTOX® to have a better trend in preventing headaches at both 3 and 6 months.

9. Page 56: Delete Reference 76 (Magalhaes E, Menezes C, Cardeal M, Melo A. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clinical Neurology and Neurosurgery. Jul 2010;112(6):463-466). The study used abobotulinumtoxinA (DYSPORT®), and not onabotulinumtoxinA (BOTOX®).

10. Page 57: Delete Reference 78 (Chankrachang S, Arayawichanont A, Poungvarin N, et al. Prophylactic botulinum type A toxin complex (Dysport®) for migraine without aura. Headache. Jan 2011;51(1):52-63). The study used abobotulinumtoxinA (DYSPORT®) and not onabotulinumtoxinA (BOTOX®).

* * * * * * * * * *

We encourage you to also review the previous clinical response we submitted on July 2, 2014, as we did not want to duplicate the evidence presentation and assessment presented in that correspondence. I hope that you have found these comments to be helpful and informative. If you have any questions, please do not hesitate to contact Karen Campbell, PharmD, Sr Manager, Scientific Services, Medical Affairs for clinical questions at 949-677-1512 or via e-mail at Campbell_Karen@allergan.com or Jonathan Kowalski, PharmD, VP US Health Outcomes for pharmacoeconomic question at 949-246-6316 or via email at Kowalski_Jonathan@allergan.com.

Regards,

Karen Campbell, PharmD AND Jonathan Kowalski, PharmD

Sr. Manager, Scientific Services VP, US Health Outcomes

Allergan Medical Affairs, Allergan, Inc Allergan, Inc

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† The current package labeling includes the following indications for BOTOX®:

1.1 Bladder Dysfunction

Overactive Bladder

BOTOX (onabotulinumtoxinA) for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

Detrusor Overactivity associated with a Neurologic Condition

BOTOX is indicated for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (e.g., SCI, MS) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

1.2 Chronic Migraine

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

Important limitations

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

1.3 Upper Limb Spasticity

BOTOX is indicated for the treatment of upper limb spasticity in adult patients, to decrease the severity of increased muscle tone in elbow flexors (biceps), wrist flexors (flexor carpi radialis and flexor carpi ulnaris) and finger flexors (flexor digitorum profundus and flexor digitorum sublimis).

Important limitations

Safety and effectiveness of BOTOX have not been established for the treatment of other upper limb muscle groups, or for the treatment of lower limb spasticity. Safety and effectiveness of BOTOX have not been established for the treatment of spasticity in pediatric patients under age 18 years. BOTOX has not been shown to improve upper extremity functional abilities, or range of motion at a joint affected by a fixed contracture. Treatment with BOTOX is not intended to substitute for usual standard of care rehabilitation regimens.

1.4 Cervical Dystonia

BOTOX is indicated for the treatment of adults with cervical dystonia, to reduce the severity of abnormal head position and neck pain associated with cervical dystonia.

1.5 Primary Axillary Hyperhidrosis

BOTOX is indicated for the treatment of severe primary axillary hyperhidrosis that is inadequately managed with topical agents.

Important limitations

The safety and effectiveness of BOTOX for hyperhidrosis in other body areas have not been established. Weakness of hand muscles and blepharoptosis may occur in patients who receive BOTOX for palmar hyperhidrosis and facial hyperhidrosis, respectively. Patients should be evaluated for potential causes of secondary hyperhidrosis (e.g., hyperthyroidism) to avoid symptomatic treatment of hyperhidrosis without the diagnosis and/or treatment of the underlying disease.

Safety and effectiveness of BOTOX have not been established for the treatment of axillary hyperhidrosis in pediatric patients under age 18.

1.6 Blepharospasm and Strabismus

BOTOX is indicated for the treatment of strabismus and blepharospasm associated with dystonia, including benign essential blepharospasm or VII nerve disorders in patients 12 years of age and above.

In addition, BOTOX® Cosmetic, which has distinct labeling, packaging and NDC-coding, has been approved by the FDA for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients, and for the temporary improvement in the appearance of moderate to severe lateral canthal lines associated with orbicularis oculi activity in adult patients. (See Tab A for a copy of the BOTOX® package insert.)

CTAF Draft Model for 20 Headache Days (Replicated Based on Draft Report)

Patient Cohort and Headache Inputs		
Chronic Migraine	1,000	
Avg Headache Days Per Month	20	
Model Time Horizon (months)	12	
Total Headaches	240000	
Botox Reduction in HA Days	9	
Placebo	6.7	
Persistent to BOTOX	96.2%	
Persistent on Placebo	100%	
Total Reduction in HA Days (Botox)	103,896	
Total Reduction in HA Days (Placebo)	80,400	
		N patients x persistence rate x reduction in HA days x model time horizon
HA Days After Treatment (Botox)	136,104	
HA Days After Treatment (Placebo)	159,600	
		Total HA days - total reduction in HA days
Treatment Cost Per Unit		
Botox (per Injection)	$1,982.00	
Treatment Cost Per Patient/Year		
Botox ($1,982/injection x 4 injections)	$7,928.00	
Placebo	$0.00	
Total Treatment Cost for Cohort		
Total Cost (Botox)	$7,702,052.00	
Total Cost (Placebo)	$0.00	
Management Cost		
Cost/Headache Day	$40.83	
Total Cost (No Treatment)	$9,799,913.00	
Total Cost (Botox)	$5,557,530.66	
Total Cost (Placebo)	$6,516,942.15	(Treatment x N patients x 1) + (Treatment x N patients x persistence rate x 3)
		(Treatment x N patients x 1) + (Treatment x N patients x persistence rate x 11)
		Cost/HA Day x HA Days After Treatment

Results vs. Placebo			
Outcome/Cost	BOTOX®	Placebo	Difference (BOTOX® - Placebo)
HA Day/Year	136,104	159,600	-23,496
Costs			
Intervention	$ 7,702,052	$0	7,702,052
Management	$5,557,531	$6,516,942	-959,411
Total	$13,259,583	$6,516,942	6,742,641
Cost/HA Day Averted			$286.97

Results vs. No Treatment			
Outcome/Cost	BOTOX®	No Treatment	Difference (BOTOX® - NoTX)
HA Day/Year	136,104	159,600	-23,496
Costs			
Intervention	$7,702,052	$0	$7,702,052
Management	$5,557,531	$9,799,913	-4,242,382
Total	$13,259,583	$9,799,913	3,459,670
Cost/HA Day Averted			$147.25

CTAF Draft Model for 15 Headache Days (Replicated Based on Draft Report)

Patient Cohort and Headache Inputs		
Chronic Migraine	1,000	
Avg Headache Days Per Month	15	
Model Time Horizon (months)	12	
Total Headaches	180000	
Botox Reduction in HA Days	9	45%
Placebo	6.7	
Persistent to BOTOX	96.2%	34%
Persistent on Placebo	100%	
Total Reduction in HA Days (Botox)	77,922	
Total Reduction in HA Days (Placebo)	60,300	
HA Days After Treatment (Botox)	102,078	
HA Days After Treatment (Placebo)	119,700	
Treatment Cost Per Unit		
Botox (per Injection)	$1,982.00	
Treatment Cost Per Patient/Year		
Botox ($1,982/injection x 4 injections)	$7,928.00	
Placebo	$0.00	
Total Treatment Cost for Cohort		
Total Cost (Botox)	$7,702,052.00	
Total Cost (Placebo)	$0.00	
Management Cost		
Cost/Headache Day	$40.83	
Total Cost (No Treatment)	$7,349,400.00	
Total Cost (Botox)	$4,167,844.74	
Total Cost (Placebo)	$4,887,351.00	

Results vs. Placebo			
Outcome/Cost	BOTOX®	Placebo	Difference (BOTOX® - Placebo)
HA Day/Year	102,078	119,700	-17,622
Costs			
Intervention	$ 7,702,052	$0	7,702,052
Management	$4,167,845	$4,887,351	-719,506
Total	$11,869,897	$4,887,351	6,982,546
Cost/HA Day Averted			$396.24

Results vs. No Treatment			
Outcome/Cost	BOTOX®	No Treatment	Difference (BOTOX® - NoTX)
HA Day/Year	102,078	119,700	-17,622
Costs			
Intervention	$7,702,052	$0	$7,702,052
Management	$4,167,845	$7,349,400	-3,181,555
Total	$11,869,897	$7,349,400	4,520,497
Cost/HA Day Averted			$256.53

CTAF Revised Model for 20 Headache Days (Replicated Based on Model Presented at CTAF Meeting)

Patient Cohort and Headache Inputs	
Chronic Migraine	1,000
Avg Headache Days Per Month	20
Model Time Horizon (months)	12
Total Headaches	240000
Botox Reduction in HA Days	9
Placebo	6.7
Persistent to BOTOX	96.2%
Persistent on Placebo	100%
Total Reduction in HA Days (Botox)	103,896
Total Reduction in HA Days (Placebo)	80,400
HA Days After Treatment (Botox)	136,104
HA Days After Treatment (Placebo)	159,600
Treatment Cost Per Unit	
Botox (per Injection)	**$1,198.33**
Placebo (per injection)	$0.00
Treatment Cost Per Patient/Year	
Botox ($1,198.33/injection x 4 injections)	**$4,793.32**
Placebo	$0.00
Total Treatment Cost for Cohort	
Total Cost (Botox)	$4,656,710.38
Total Cost (Placebo)	$0.00
Management Cost	
Cost/Headache Day	$40.83
Total Cost (No Treatment)	$9,799,200.00
Total Cost (Botox)	$5,557,126.32
Total Cost (Placebo)	$6,516,468.00

Results vs. Placebo			
Outcome/Cost	BOTOX®	Placebo	Difference (BOTOX® - Placebo)
HA Day/Year	136,104	159,600	-23,496
Costs			
Intervention	$4,656,710	$0	$4,656,710
Management	$5,557,126	$6,516,468	-$959,342
Total	$10,213,837	$6,516,468	$3,697,369
Cost/HA Day Averted			$157.36

Results vs. No Treatment			
Outcome/Cost	BOTOX®	No Treatment	Difference (BOTOX® - NoTX)
HA Day/Year	136,104	240,000	-103,896
Costs			
Intervention	$4,656,710	$0	4,656,710
Management	$5,557,126	$9,799,200	-4,242,074
Total	$10,213,837	$9,799,200	414,637
Cost/HA Day Averted			$3.99

CTAF Revised Model for 15 Headache Days (Replicated Based on Model Presented at CTAF Meeting)

Patient Cohort and Headache Inputs		
Chronic Migraine	1,000	
Avg Headache Days Per Month	15	
Model Time Horizon (months)	12	
Total Headaches	180000	
Botox Reduction in HA Days	9	45%
Placebo	6.7	
Persistent to BOTOX	96.2%	34%
Persistent on Placebo	100%	
Total Reduction in HA Days (Botox)	77,922	
Total Reduction in HA Days (Placebo)	60,300	
HA Days After Treatment (Botox)	102,078	
HA Days After Treatment (Placebo)	119,700	
Treatment Cost Per Unit		
Botox (per Injection)	**$1,198.33**	
Treatment Cost Per Patient/Year		
Botox ($1,982/injection x 4 injections)	**$4,793.32**	
Placebo	$0.00	
Total Treatment Cost for Cohort		
Total Cost (Botox)	$4,656,710.38	
Total Cost (Placebo)	$0.00	
Management Cost		
Cost/Headache Day	$40.83	
Total Cost (No Treatment)	$7,349,400.00	
Total Cost (Botox)	$4,167,844.74	
Total Cost (Placebo)	$4,887,351.00	

Results vs. Placebo			
Outcome/Cost	BOTOX®	Placebo	Difference (BOTOX® - Placebo)
HA Day/Year	102,078	119,700	-17,622
Costs			
Intervention	$ 4,656,710	$0	4,656,710
Management	$4,167,845	$4,887,351	-719,506
Total	$8,824,555	$4,887,351	3,937,204
Cost/HA Day Averted			$223.43

Results vs. No Treatment			
Outcome/Cost	BOTOX®	No Treatment	Difference (BOTOX® - NoTX)
HA Day/Year	102,078	180,000	-77,922
Costs			
Intervention	$4,656,710	$0	$4,656,710
Management	$4,167,845	$7,349,400	-3,181,555
Total	$8,824,555	$7,349,400	1,475,155
Cost/HA Day Averted			$18.93

CTAF Revised Model for 20 Headache Days With Adjustment for Sham Placebo Injection Cost

Patient Cohort and Headache Inputs	
Chronic Migraine	1,000
Avg Headache Days Per Month	20
Model Time Horizon (months)	12
Total Headaches	240000
Botox Reduction in HA Days	9
Placebo	6.7
Persistent to BOTOX	96.2%
Persistent on Placebo	100%
Total Reduction in HA Days (Botox)	103,896
Total Reduction in HA Days (Placebo)	80,400
HA Days After Treatment (Botox)	136,104
HA Days After Treatment (Placebo)	159,600
HA Days No Treatment	240,000
Treatment Cost Per Unit	
Botox (per Injection)	**$1,198.33**
Placebo (per injection)	$103.87
Treatment Cost Per Patient/Year	
Botox ($1,198.33/injection x 4 injections)	**$4,793.32**
Placebo	$415.48
Total Treatment Cost for Cohort	
Total Cost (Botox)	$4,656,710.38
Total Cost (Placebo)	$415,480.00
Management Cost	
Cost/Headache Day	$40.83
Total Cost (No Treatment)	$9,799,913.00
Total Cost (Botox)	$5,557,530.66
Total Cost (Placebo)	$6,516,942.15

Results vs. Placebo			
Outcome/Cost	BOTOX®	Placebo	Difference (BOTOX® - Placebo)
HA Day/Year	136,104	159,600	-23,496
Costs			
Intervention	$4,656,710	$415,480	$4,241,230
Management	$5,557,531	$6,516,942	-$959,411
Total	$10,214,241	$6,932,422	$3,281,819
Cost/HA Day Averted			$139.68

Results vs. No Treatment			
Outcome/Cost	BOTOX®	No Treatment	Difference (BOTOX® - NoTX)
HA Day/Year	136,104	240,000	-103,896
Costs			
Intervention	$4,656,710.38	$0	4,656,710
Management	$5,557,531	$9,799,913	-4,242,382
Total	$10,214,241	$9,799,913	414,328
Cost/HA Day Averted			$3.99

CTAF Revised Model for 15 Headache Days With Adjustment for Sham Placebo Injection Cost

Patient Cohort and Headache Inputs			
Chronic Migraine	1,000		
Avg Headache Days Per Month	15		
Model Time Horizon (months)	12		
Total Headaches	180000		
Botox Reduction in HA Days	9	45.0%	
Placebo	6.7		
Persistent to BOTOX	96.2%	33.5%	
Persistent on Placebo	100%		
Total Reduction in HA Days (Botox)	77,922		
Total Reduction in HA Days (Placebo)	60,300		
HA Days After Treatment (Botox)	102,078		
HA Days After Treatment (Placebo)	119,700		
HA Days No Treatment	180,000		
Treatment Cost Per Unit			
Botox (per Injection)	**$1,198.33**		
Placebo (per injection)	$103.87		
Treatment Cost Per Patient/Year			
Botox ($1,198.33/injection x 4 injections)	**$4,793.32**		
Placebo	$415.48		
Total Treatment Cost for Cohort			
Total Cost (Botox)	$4,656,710.38		
Total Cost (Placebo)	$415,480.00		
Management Cost			
Cost/Headache Day	$40.83		
Total Cost (No Treatment)	$7,349,400.00		
Total Cost (Botox)	$4,167,844.74		
Total Cost (Placebo)	$4,887,351.00		

Results vs. Placebo			
Outcome/Cost	BOTOX®	Placebo	Difference (BOTOX® - Placebo)
HA Day/Year	102,078	119,700	-17,622
Costs			
Intervention	$4,656,710	$415,480	$4,241,230
Management	$4,167,845	$4,887,351	-$719,506
Total	$8,824,555	$5,302,831	$3,521,724
Cost/HA Day Averted			$199.85

Results vs. No Treatment			
Outcome/Cost	BOTOX®	No Treatment	Difference (BOTOX® - NoTX)
HA Day/Year	102,078	180,000	-77,922
Costs			
Intervention	$4,656,710.38	$0	4,656,710
Management	$4,167,845	$7,349,400	-3,181,555
Total	$8,824,555	$7,349,400	1,475,155
Cost/HA Day Averted			$18.93

CTAF Revised Model for 20 Headache Days With Adjustment for Sham Placebo Injection Cost and Corrected Persistence

Patient Cohort and Headache Inputs	
Chronic Migraine	1,000
Avg Headache Days Per Month	20
Model Time Horizon (months)	12
Total Headaches	240000
Botox Reduction in HA Days	9
Placebo	6.7
Persistent to BOTOX	**88.2%**
Persistent on Placebo	**90.4%**
Total Reduction in HA Days (Botox)	95,256
Total Reduction in HA Days (Placebo)	72,682
HA Days After Treatment (Botox)	144,744
HA Days After Treatment (Placebo)	167,318
Treatment Cost Per Unit	
Botox (per Injection)	**$1,198.33**
Placebo	**$103.87**
Treatment Cost Per Patient/Year	
Botox ($1,982/injection x 4 injections)	$4,793.32
Placebo	$415.48
Total Treatment Cost for Cohort	
Total Cost (Botox)	$4,369,111.18
Total Cost (Placebo)	$385,565.44
Management Cost	
Cost/Headache Day	$40.83
Total Cost (No Treatment)	$9,799,913.00
Total Cost (Botox)	$5,910,327.53
Total Cost (Placebo)	$6,832,107.35

Results vs. Placebo			
Outcome/Cost	BOTOX®	Placebo	Difference (BOTOX® - Placebo)
HA Day/Year	144,744	167,318	-22,574
Costs			
Intervention	$4,369,111.18	$385,565	3,983,546
Management	$5,910,328	$6,832,107	-921,780
Total	$10,279,439	$7,217,673	3,061,766
Cost/HA Day Averted			$135.63

Results vs. No Treatment			
Outcome/Cost	BOTOX®	No Treatment	Difference (BOTOX® - NoTX)
HA Day/Year	144,744	240,000	-95,256
Costs			
Intervention	$4,369,111.18	$0	4,369,111
Management	$5,910,328	$9,799,913	-3,889,585
Total	$10,279,439	$9,799,913	479,526
Cost/HA Day Averted			$5.03

CTAF Revised Model for 15 Headache Days With Adjustment for Sham Placebo Injection Cost and Corrected Persistence

Patient Cohort and Headache Inputs

Chronic Migraine	1,000		
Avg Headache Days Per Month	15		
Model Time Horizon (months)	12		
Total Headaches	180000		
Botox Reduction in HA Days	9	45%	
Placebo	6.7		
Persistent to BOTOX	**88.2%**	33.50%	
Persistent on Placebo	**90.4%**		
Total Reduction in HA Days (Botox)	71,442		
Total Reduction in HA Days (Placebo)	54,511		
HA Days After Treatment (Botox)	108,558		
HA Days After Treatment (Placebo)	125,489		

Treatment Cost Per Unit

Botox (per Injection)	**$1,198.33**
Placebo	**$103.87**

Treatment Cost Per Patient/Year

Botox ($1,982/injection x 4 injections)	$4,793.32
Placebo	$415.48

Total Treatment Cost for Cohort

Total Cost (Botox)	$4,369,111.18
Total Cost (Placebo)	$385,565.44

Management Cost

Cost/Headache Day	$40.83
Total Cost (No Treatment)	$7,349,400.00
Total Cost (Botox)	$4,432,423.14
Total Cost (Placebo)	$5,123,707.70

Results vs. Placebo

Outcome/Cost	BOTOX®	Placebo	Difference (BOTOX® - Placebo)
HA Day/Year	108,558	125,489	-16,931
Costs			
Intervention	$4,369,111.18	$385,565	3,983,546
Management	$4,432,423	$5,123,708	-691,285
Total	$8,801,534	$5,509,273	3,292,261
Cost/HA Day Averted			$194.45

Results vs. No Treatment

Outcome/Cost	BOTOX®	No Treatment	Difference (BOTOX® - NoTX)
HA Day/Year	108,558	180,000	-71,442
Costs			
Intervention	$4,369,111.18	$0	4,369,111
Management	$4,432,423	$7,349,400	-2,916,977
Total	$8,801,534	$7,349,400	1,452,134
Cost/HA Day Averted			$20.33