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To:	rporteno@chpnet.org
CC:	Shiva Noorchashm
Sent:	4/24/2009 8:54:15 PM
Subject:	FENTORA Medical/Scientific Advisory Board
Attachments:	Exec summary ver 14.doc

Dear Dr. Portenoy:

It was a pleasure to work with you to make the FENTORA Medical/Scientific Advisory Board a success. Thanks for all your help. Please see attached document which is an executive summary of the advisory board. After we obtain your comments and incorporate them, we plan to send this document to the other advisors. Shiva will be following up with you to see if you have any comments on this document. Have a great weekend. Arvind

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Executive Summary for April 1, 2009 Medical/Scientific Advisory Board

1. **FENTORA® update:**
The purpose of this section was to summarize the FENTORA Noncancer Clinical Development Plan. Most advisor discussion focused on the issues of abuse and overdose with FENTORA and the FDA Controlled Substance Staff's position on these issues. Advisors believe it is difficult to extrapolate abuse liability from clinical trial data to the real-world setting. They cautioned the company to be careful in using its own clinical study data, as well as comparisons to other companies' clinical trial data to predict postmarketing abuse liability. Next, the long-term safety study left many questions unanswered (e.g., true reasons for drop-outs) and raised more questions. Finally, the advisors felt that FENTORA is a difficult drug to prescribe given that the instructions for safe use are significant. Some patients may not be able to understand proper instructions even after extensive counseling.

2. **FENTORA REMS discussion:**
During this session, the finalized REMS proposal, which was submitted to the FDA on April 2nd, was reviewed and discussed with the advisors. It was communicated at the outset that, due to the submission deadline, advisor feedback would not inform the current submission document sent to the FDA. However, feedback from advisors was sought regarding implementation of the REMS and the ability to partner with clinicians, thought leaders, and key pain-related societies.

Dr. Nathaniel Katz first provided an overview of the regulatory context for opioids, more specifically FDA's position on the implementation of REMS programs as first described in the FDA Amendments Act of 2007. Based on the learnings from the Accutane® (isotretinoin, Roche) registration system, the FDA will likely want to understand the percentage of total prescriptions dispensed outside the REMS program. He also noted that pharmacists in general found the interactive voice response system with the Accutane system less than ideal. He indicated that the current model used for Accutane will be hard to scale up to cover products with a much greater volume of prescriptions, such as Schedule II controlled release products.

Overall the advisors felt that the FENTORA REMS program, as well as potential REMS programs for schedule II controlled-release opioids and methadone, will restrict access for appropriate patients. The advisors noted that various physician groups and patient associations will be crafting strategies that will most likely recommend against the use of REMS for opioids in pain management. This will be discussed at a meeting on April 29 with several professional and patient advocacy associations, including the American Medical Association. Advisors felt that many current FENTORA prescribers would not be willing to register in the REMS program and, for those willing to register, their threshold for prescribing FENTORA will be higher, resulting in fewer patients being prescribed the product.

It was recommended that Cephalon gain a greater understanding of the level of satisfaction with FENTORA therapy prior to implementation of the registration system and then repeat the satisfaction survey after the registration system is in place. In addition, a pre- and post-implementation study on health outcomes would be helpful to assess whether restrictions to prescribing some but not all opioids would lead to a shift of adverse outcomes and aberrant

behavior from one group of opioids to another. Advisors recommended that the company look into ways to offer continuing medical education credits as part of the mandatory educational component of the registration system, as is the case with the buprenorphine performance access system.[1] Overall, the quarterly confirmation of safe use conditions for each patient within the REMS was viewed as too burdensome and did not make sense in the context of daily patient flows. Advisors recommended a simplified system in which they would be able to check a box when writing each prescription for FENTORA. Finally, it was also recommended to avoid any perception of shift in liability to the provider (e.g. the Physician-Patient agreement) or involvement by the company with clinical care, for example in the execution of the chart review study. Otherwise some institutions may not allow the HCP to participate in the REMS program.

3. **Discussion of breakthrough pain disease state:**
The objectives of this section were to obtain advisor input regarding Cephalon's current communications regarding breakthrough cancer pain, and to seek their feedback on epidemiology and functional/economic impact data of breakthrough pain in noncancer populations. Advisors commented that there is a need for more data on the impact of breakthrough pain in cancer as well as noncancer patients. Because the overall prevalence from the surveys may overstate the clinical significance of the breakthrough pain, they stressed that not all breakthrough pain episodes require treatment with a rapid onset opioid. The company should proactively discuss that there are certain patients who may be reasonable candidates for long-acting opioids and traditional short-acting opioids, but who may be at too high a risk for rapid onset opioids. In addition, they recommended that the company discuss assessment and treatment of breakthrough pain as part of the overall treatment strategy for chronic pain, including treatment of the persistent pain.

At the May 6, 2008 FDA Advisory Board meeting, as well as in other communications, several physicians questioned the existence/importance of breakthrough pain in noncancer populations. The company and the medical community in general needs to gain a greater understanding of these perspectives and develop a strategy to better communicate the total burden of illness of breakthrough pain in noncancer chronic pain populations. Concerns regarding hyperalgesia, neuroendocrine effects, and addiction are all more important now than they were several years ago.

The panel reviewed the Cephalon-sponsored burden of illness study proposal, designed to better understand the true economic and functional burden of illness of breakthrough pain in opioid-tolerant noncancer pain patients. The advisors felt that the proposal, in theory, has great potential, but significant thought would still be required on study methodology, including control groups. Advisors provided feedback on thresholds for opioid tolerance and noted that patients taking less than 60 mg of morphine equivalents daily should be included. Chronic non-cancer pain patients on opioids who have breakthrough pain should be compared to patients on opioids who do not have breakthrough pain. Likewise, another comparison could be made between chronic pain patients with or without breakthrough pain and not using opioids. It was noted that

[1] Post-meeting note: upon further evaluation, Cephalon found that the education program for buprenorphine takes about 8 hours to complete, and is conducted by a third party without involvement of the manufacturer. The educational module for the FENTORA REMS will last between 5 and 10 minutes and its content will be entirely controlled by Cephalon. Thus it will not lend itself to accreditation.

outpatients insured through employment based health plans aren't necessarily representative of the entire population of patients.

The vendor may consider sending a letter to the patient giving them an option to "opt out" (as opposed to opt in). The advisors felt that it will be acceptable to do this survey without IRB approval. It would be a good idea to send a letter outlining the time needed for the phone survey. Given the phone survey may take approximately 30 minutes to complete, it may be good to split it into 2 separate phone interviews to obtain the most accurate and meaningful data.

4. **FENTORA phase IV studies:**

In this final section of the advisory board meeting, 2 phase IV study proposals were presented for advisor input. The first study examines the overall question of whether a long-acting opioid alone can successfully treat both persistent pain and breakthrough pain. The advisors felt that this study addresses a very important scientific issue but there would be significant methodological issues. For instance, some patient's histories may reveal that they are unable to tolerate an increase in the long-acting opioid. The recommendation was to examine a population of patients who recently began using opioid therapy for chronic, noncancer pain and have breakthrough pain. This study could be blinded potentially, if patients were restricted to using one type of long-acting agent, such as Duragesic® (fentanyl transdermal system, Ortho-McNeil) or OxyContin® (oxycodone HCl, Purdue Pharma). The company needs to understand the dosages achieved in the OPANA® (oxymorphone HCl, Endo Pharmaceuticals) and OxyContin studies.

The second study compares a rapid onset opioid in a structured treatment protocol to a traditional short-acting opioid for the treatment of breakthrough pain. Overall, the advisors were unclear on the clinical significance of this type of study. They noted various methodological limitations and felt it may be difficult to put into a protocol the complex thought processes that underlie specific decisions that physicians have to make. The advisors suggested several methodologies (e.g. Propensity Scoring) to potentially address these issues. The propensity scoring model requires an *a priori* understanding of the key predictors and baseline variables. The model also has a degree of complexity that is difficult to explain in a publication. Finally, understanding the predictive ability of the chemical coping scale in a group of patients who already are screened based on recent history of substance abuse would enable further refinement of the population in which FENTORA should be used. Overall, there was no overwhelming support for moving forward with either of the 2 studies.