

Food and Drug Administration
Center for Drug Evaluation and Research
5630 Fishers Lane, Room 1066, Rockville, Maryland 20857

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee
meeting on March 7 & 8, 2006:

The committee discussed Tysabri (Natalizumab) biologic license application 125104/15; Biogen Idec Inc. for an indication in patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The committee will discuss the risks (including progressive multifocal leukoencephalopathy (PML)) associated with Tysabri administration, the efficacy of Tysabri in the treatment of multiple sclerosis relapses and/or disability, the possible return of Tysabri to the marketplace, and proposed risk management plan(s) for Tysabri.

These summary minutes for the March 7 & 8, 2006 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee were approved on March 14, 2006.

I certify that I attended the March 7 & 8, 2006 meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and that these minutes accurately reflect what transpired.

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Lt. Sohail Mosaddegh, Pharm.D., RPh.
Acting Executive Secretary, PCNS

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Karl Kieburtz, M.D., M.P.H.
Chair, PCNS

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information Office.

Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA and from the Sponsor. The meeting was called to order by Karl Kieburtz, M.D., M.P.H. (Committee Chair); the conflict of interest statement was read into the record by Lt. Sohail Mosaddegh, Pharm.D., R.Ph. (Acting Executive Secretary). There were approximately 300 persons in attendance. There were 36 speakers for the Open Public Hearing sessions.

Attendance:

Peripheral and Central Nervous System Drugs Advisory Committee Member:

Karl D. Kieburtz, M.D., M.P.H., Larry B. Goldstein, M.D., Steven T. DeKosky, M.D., Michael D. Hughes, Ph.D., Ralph L. Sacco, M.D., M.S., James R. Couch Jr., M.D., Ph.D., F.A.C.P., Lily K.F. Jung, M.D., M.M.M.

Peripheral and Central Nervous System Drugs Advisory Committee Consultant (voting):

Carol Koski, M.D., Cynthia Sitcov, James Sejvar M.D. (Federal Employee)

Anesthetic and Life Support Drugs Advisory Committee (voting)

Justin C. McArthur, M.D.

Drug Safety and Risk Management Advisory Committee (Voting):

George Ricaurte, M.D., Ph.D.

Peripheral and Central Nervous System Drugs Advisory Committee (non-voting):

Roger Porter, M.D.

FDA Participants:

Russell Katz, M.D., Marc Walton, Ph.D., M.D., Susan McDermott, M.D., Alice Hughes, M.D., Robert Temple, M.D., Gerald Dal Pan, M.D., MHS, Douglas Throckmorton, M.D., Diane Wysowski, Ph.D.

Open Public Hearing Speakers:

Alison Kutler, Audrey Ann Greenfeld, Barbara Sales, Barbara Crooks, Bartira Tiburtius, Carol Fuquay (Via Video), Charlie Richardson, Cheryl Bloom, Christopher Hughes, Christy Cooksey, Clive Milton, David Smith, David Miller, Doug Franklin, Emily Canavan, Frank Burroughs, Heather Smith, Jack Calfee, Jason Mark, John Richert, K.P. Lyons, Karen Miller, Larry P. Keller, Lauren Roberts (Via Video), Linda Lyons, Lisa Casanova, Alex MacDonald, Marcy Canavan, Mark Godec, Martha Rogers, Michael Kahn, Mike Barron, Pamela Sue Clark, Peter Wade, Sonda Lawson, Stan Croydon, Stephen Melvin Lore, Steven Triedman, Virginia Ladd, William Stuart.

Issue: The committee will discuss Tysabri (Natalizumab) biologic license application 125104/15; Biogen Idec Inc. for an indication in patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. The committee will discuss the risks (including progressive multifocal leukoencephalopathy (PML)) associated with Tysabri administration, the efficacy of Tysabri in the treatment of multiple sclerosis relapses and/or disability, the possible return of Tysabri to the marketplace, and proposed risk management plan(s) for Tysabri.

The agenda was as follows:

March 7, 2006

Introduction

Russell Katz, M.D.
Director, Division
Division of Anti-Infective and Ophthalmology Products
CDER, FDA

Sponsor Presentations (Biogen-Idec Inc.)

Introduction

Burt Adelman, M.D.
Executive Vice President, Development

Efficacy Data	Biogen Idec Inc. Alfred Sandrock, M.D., Ph.D. Vice President, Neurology Biogen Idec Inc.
Safety Data	Michael Panzara, M.D., M.P.H. Vice President, Neurology Biogen Idec Inc.
Risk-Management Plan	Carmen Bozic, M.D. Vice President, Drug Safety and Risk Management Biogen Idec Inc.
Clinical Perspective	Richard A. Rudick, M.D. Director, The Mellen Center Chairman, Division of Clinical Research Cleveland Clinic Foundation Committee questions to the sponsor

Food and Drug Administration Presentation

Background, Efficacy and PML	Susan McDermott, M.D. Clinical Reviewer, DNP, FDA
Safety	Alice Hughes, M.D. Clinical Safety Reviewer, DNP, FDA
Risk Minimization Action Plan	Diane Wysowski, Ph.D. Reviewer, Office of Drug Safety, FDA

Committee Questions to the FDA

Open Public Hearing

The committee adjourned at approximately 4:00 P.M.

Agenda March 8, 2006

Committee Discussion

Questions to the Committee

Questions to the Committee:

1. Has Biogen demonstrated natalizumab's efficacy on reduced frequency of relapses through two years, and fulfilled the commitment made under the Accelerated Approval regulations to verify the sustained clinical benefit?
After discussion the committee consensus was that Biogen has demonstrated natalizumab's efficacy on reducing the frequency of relapses through two years and fulfilled their commitment made under the Accelerated Approval regulations.
2. Has Biogen demonstrated efficacy on reduced accumulation of physical disability?
After discussion the committee consensus was that Biogen has demonstrated efficacy on reducing the accumulation of physical disability.
3. Outside of PML, are there safety-related issues associated with use of natalizumab that you consider to be important considerations in making a risk-benefit assessment, including:
 - a. Non-infectious disease risks?
After significant discussion the committee consensus was that hypersensitivity reactions and development of antibodies were important considerations in making a risk-benefit assessment.

- b. Non-PML infectious disease risks (e.g., opportunistic infections, herpes CNS infections)?
After significant discussion the committee consensus was that there is some concern of serious viral infections.
4. PML has been observed in the multiple sclerosis (MS) population only in patients concomitantly receiving Avonex, and in a patient with Crohn's disease who had a complex recent and prior history of immunosuppressive agent exposure. Do you believe that the natalizumab-associated risk of PML is entirely limited to patients concomitantly (or recently) exposed to a second immunosuppressive agent?
After some discussion the committee consensus was that the risk of PML is not limited to patients concomitantly (or recently) exposed to a second immunosuppressive agent.
5. Are there additional data (or studies) that you recommend FDA obtain prior to determining whether natalizumab may return to the marketplace? If so, please describe the necessary data (or study).
After some discussion the committee consensus was that they did not need additional data on determining whether natalizumab may return to the marketplace.
6. If natalizumab returns to commercial distribution, are there specific subsets of the relapsing MS population for whom you would consider natalizumab use either reasonable or inappropriate? Please discuss, for example:
- a. Patients with MS who have not tried any of the other available first-line therapies (interferon beta or glatiramer acetate)
After significant debate the chair polled the committee members on 4 questions. These were polls to see if the committee was at a consensus and was not an official vote.
Should natalizumab be permitted as first line therapy?
YES: 7 NO: 5
- b. Patients with MS who are above or below a specific level of disability or have some other specific disease-related criteria
The second poll was is there an upper level of disability that would be a consideration in the use of natalizumab?
YES: 1 NO: 11
The third poll was is there a lower level of disability that would be a consideration in the use of natalizumab?
YES: 1 NO: 10 ABSTAIN: 1
- c. Patients with MS who have tried one (or more) of the other available therapies and have continued to have a specified frequency of relapses or rate of disability increase
(See transcripts for detailed discussion)
- d. Patients with MS who have tried one of the available therapies and been unable to continue treatment due to intolerability of adverse effects
(See transcripts for detailed discussion)
- e. Patients with MS who have received one of the available therapies and plan to continue that therapy while receiving natalizumab. Please discuss each of the available therapies (i.e., Avonex, Betaseron, Copaxone, Rebif, and Novantrone) separately.
After some discussion a fourth poll was taken. Should natalizumab be taken with betaseron, Copaxone, Rebif, or Novantrone?
YES: 0 NO: 12
The committee also came to the consensus that a wash out period would be needed if switching to natalizumab from one of these medications.
7. Considering the currently available data, please discuss whether natalizumab should be returned to the marketplace for at least some patients, taking into account the preceding discussion of specific populations. After discussion, please vote on this question.
This question was voted on.
YES: 12 NO: 0

8. If the answer to Question 7 above is in favor of return to commercial availability, and natalizumab returns to the marketplace at this time, please discuss what you consider to be the essential or non-essential features of an acceptable risk management (minimization) plan. In this discussion, consider the risk management plan proposed by the sponsor, and comment on the appropriateness of specific aspects of the proposed plan. Please include in your discussion potential restrictions to patient availability, such as:

- a. Patient registry with distribution restricted to only patients enrolled in the registry

What information (e.g., deaths, PML, other infections, serious adverse events, concomitant immunomodulators), if any, is it essential to obtain on all patients who receive Tysabri?

The committee discussed the matter and the overall consensus was that the proposed information from the sponsor was necessary but some of the members wanted more information. There was no clear consensus on the extra information that would be needed. (See transcripts for detailed discussion)

- b. Patient observational study

1. What additional information, if any, is it important to obtain in a subset of patients who receive Tysabri (i.e., an observational study that is more intensive than the registry)?

After much debate the general consensus of the committee was that there are some additional questions that the committee thinks are worth addressing but are more appropriate in the context of a research study rather than mandatory as part of clinical care. (See transcripts for detailed discussion)

2. If an observational study is appropriate, how large should the observational study be?
(See transcripts for detailed discussion)

- c. Restrictions on distribution system

1. Should each vial be distributed using a 1:1 system so that every shipped vial is designated for administration to a specific patient?

The general consensus of the committee was that there should be some restriction on the distribution but not on a 1:1 basis. There should also be some mandatory monthly reporting back about the use of the checklists. (See transcripts for detailed discussion)

2. Should infusion centers be permitted to maintain a stock of natalizumab that is not designated for any specific subject?
(See transcripts for detailed discussion)

3. Should only a single dose be shipped at any one time, with shipment of the subsequent dose dependent on receiving some information back from the infusion center? If so, what information (e.g., physical exam, immunosuppression checklist, PML symptom checklist) should be necessary to prompt distribution of the next dose?
(See transcripts for detailed discussion)

4. Should there be a periodic reauthorization of Tysabri administration? If so, how often (e.g., prior to each infusion, every 6 months), and by whom (e.g., infusion center nurse, patient's physician)?
(See transcripts for detailed discussion)

5. Does the patient's neurologist need to examine the patient with some frequency and re-prescribe Tysabri? If so, what frequency is appropriate?
(See transcripts for detailed discussion)

- d. Restriction to only MS patients

This question was discussed by the committee earlier as part of question 6 and the committee's consensus was that Tysabri be used only in MS patients. (See transcripts for detailed discussion)

e. Restriction to only MS patients for whom natalizumab was deemed appropriate in the answer to Question 7
(See transcripts for detailed discussion)

f. Immunosuppression checklist

1. Is an immunosuppression checklist appropriate?

(See transcripts for detailed discussion)

2. If a checklist is required, what are essential elements of this checklist?

(See transcripts for detailed discussion)

3. Who should administer the checklist, and how often? *(See transcripts for detailed discussion)*

(See transcripts for detailed discussion)

4. Is any other monitoring of immunosuppression necessary prior to each infusion? Or at some other time interval

(See transcripts for detailed discussion)

g. PML checklist

1. Is a PML symptom checklist appropriate?

(See transcripts for detailed discussion)

2. If a checklist is required, what are essential elements of this checklist?

(See transcripts for detailed discussion)

3. Who should administer the checklist, and how often?

(See transcripts for detailed discussion)

4. Is any additional monitoring for PML necessary prior to each infusion? Or at some other time interval?

(See transcripts for detailed discussion)

There was a great deal of debate on these questions but the general consensus was that with regards to PML any observed or reported exacerbation would be treated as though it could be a new case of PML and evaluated as such. *(See transcripts for detailed discussion)*

h. Other potential requirements for ongoing monitoring while receiving natalizumab, including, but not limited to:

1. JC Virus assay in serum and/or cerebrospinal fluid

(See transcripts for detailed discussion)

2. MRI of brain

(See transcripts for detailed discussion)

3. Quantitative cognitive testing or brief cognitive screening questionnaire

(See transcripts for detailed discussion)

4. Periodic full neurologic exam or brief physical function questionnaire

(See transcripts for detailed discussion)

9. For subjects who received natalizumab in clinical trials, and who have not received natalizumab for at least 1 year (or longer), do you recommend any further monitoring? If so, what monitoring procedures and what duration of monitoring do you recommend?

The committee came to the consensus that annual monitoring should be done for two to three years after natalizumab therapy is stopped. *(See transcripts for detailed discussion)*

10. If the answer to Question 7 above is in favor of return to commercial availability, and natalizumab returns to the marketplace at this time, please discuss the following:
- a. If a patient discontinues natalizumab, what monitoring procedures and what duration of monitoring after discontinuation do you recommend? **The committee came to the consensus that annual monitoring should be done for two to three years after natalizumab therapy is stopped.**
 - b. If a patient discontinues natalizumab and plans to initiate treatment with another immune-modulating agent (e.g., an interferon beta or glatiramer acetate), do you recommend that the patient wait for some period of time before initiating the interferon beta or glatiramer acetate? If so, how long?
The committee agreed that there needed to be a wash out period but due to lack of evidence a firm time period could not be given. The periods discussed as recommendations were two weeks and two to three months
 - c. If a patient discontinues an immune-modulating agent (e.g., either an interferon beta or glatiramer acetate) and plans to initiate treatment with natalizumab, do you recommend that the patient wait for some period of time before initiating natalizumab? If so, how long?
The committee agreed that there needed to be a wash out period but due to lack of evidence a firm time period could not be given. The periods discussed as recommendations were two weeks and two to three months
11. The two PML infections observed in MS patients were both in patients receiving natalizumab and Avonex concurrently, suggesting the possibility that PML risk is greater in patients receiving concurrent treatment. Furthermore, while Study 1802 indicated that natalizumab added to Avonex provides additional benefit, it is unknown whether Avonex provides any additional benefit when added to natalizumab treatment. If, in the preceding discussion, you have advised that use of marketed natalizumab be recommended only for monotherapy, please discuss if, and when, exploration of the safety and efficacy of concurrent use of natalizumab with Avonex, or any other interferon beta should be evaluated. Please include in your discussion the options of:
- a. Never risk concurrent use
 - b. Evaluation of concurrent use in clinical trials only after the risk of PML or other infections in monotherapy is better quantified
After discussion regarding choices 11a, 11b, 11c, and 11d all committee members chose option 11b.
 - c. Evaluation of concurrent use in clinical trials is acceptable at the present time
 - d. Any other approaches to improved understanding of the risk-benefit comparison of concurrent use you wish to recommend

(See transcripts for detailed discussion)