Questions to Advisory Committee

FDA requests that the Advisory Committee (AC) discuss the following questions. However, FDA also encourages the AC to discuss any other issues that the AC members believe are relevant to the current submission.

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?

2. Has Biogen demonstrated efficacy on reduced 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?

    b. Non-PML infectious disease risks (e.g., opportunistic infections, herpes CNS 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?

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).

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)

    b. Patients with MS who are above or below a specific level of disability or have some other specific disease-related criteria

    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

d. Patients with MS who have tried one of the available therapies and been unable to continue treatment due to intolerability of adverse effects

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.

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.

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. 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

   b. Restriction to only MS patients

   c. Restriction to only MS patients for whom natalizumab was deemed appropriate in the answer to Question 7

   And potential requirements for ongoing monitoring while receiving natalizumab, including, but not limited to:

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

   e. MRI of brain

   f. Quantitative cognitive testing or brief cognitive screening questionnaire

   g. Periodic full neurologic exam or brief physical function questionnaire

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?

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?

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?

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?

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

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