Joint Meeting of the Gastrointestinal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

July 31, 2007

Tysabri (natalizumab) for Crohn's Disease

Questions to the Advisory Committee

1. The proposed indication states that "Tysabri is indicated for inducing and maintaining sustained response and remission, and eliminating corticosteroid use in patients with moderately to severely active Crohn's disease with inflammation, as evidenced by elevated CRP level or another objective marker."

   Do the available data support the efficacy of Tysabri in patients with moderately to severely active Crohn's disease (CD) with inflammation, as evidenced by elevated CRP level or another objective marker:

   a. For the induction of sustained response and remission?
   b. For the maintenance of sustained response and remission?
   c. In eliminating corticosteroid use?
   d. Is elevated CRP level a logical or clinically meaningful restriction?

2. The proposed indication also states that Tysabri is "generally recommended for patients who have had an inadequate response to, or are unable to tolerate conventional Crohn's disease therapies."

   a. Do the available data support the efficacy of Tysabri in this patient population?

   b. Is there a subset of the CD population in which the increased risk of PML in patients taking Tysabri might be acceptable? Please discuss the following candidate CD patient populations:

      1) Inadequate response to other available commonly used individual and combined treatments (5-ASAs, steroids, azathioprine, 6-MP, methotrexate, infliximab, adalimumab). Specify which individual or combined treatments.
      2) Specific level of disease severity. Specify criteria.
      3) Other disease characteristics or potential benefits that make the risks acceptable. Specify what these would be.

   c. For the subgroups designated above please discuss:

      1) Whether these subgroups have been adequately identified and described in the clinical studies
      2) Whether the currently available exploratory analysis of those subgroups provides adequate support for your recommendation.

3. Are there sufficient data to support maintenance therapy of CD with monotherapy versus combined treatment with corticosteroids and/or immunosuppressants?

Questions to the Advisory Committee

4. a. What risks associated with the use of Tysabri in Crohn's disease are important for a risk-benefit assessment (e.g. PML, hypersensitivity, infection, malignancy, other)?

   b. How might these risks be impacted by current CD treatment strategies for induction and maintenance (e.g. 'step-up', 'top-down", steroid sparing)?

5. Considering the currently available data, and taking into account the preceding discussion of specific populations, proposed use, and anticipated risks, are there additional:

   a. Efficacy data (studies) that should be obtained prior to approving Tysabri for Crohn's disease? If so, please describe.

   b. Safety data (studies) that should be obtained prior to approving Tysabri for Crohn's disease? If so, please describe.

6. Commonly used therapies for CD include corticosteroids, immunosuppressants, and/or biological agents (e.g. TNF-alpha blockers). If Tysabri were to be approved for Crohn's disease:

   a. Should treatment with Tysabri be prohibited based on duration of <u>prior use</u> and/or total doses of these therapies?
      1) What should the washout period be for <u>prior use</u>? Respond for each of the therapies.

   b. What should the period of <u>concomitant use</u> of steroids be?
      1) Is six months for steroid tapering acceptable?
      2) What should the maximum period of concomitant steroid use be for CD flares?

   c. Do you recommend use of any other concomitant therapy besides steroids for CD flares (e.g. immunosuppressants, or anti-TNF agents)?

7. If Tysabri were to be approved for Crohn's disease, what specific requirements, if any, would you recommend for CD patients, either upon initiation of Tysabri or for ongoing monitoring? In particular, please discuss:

   a. MRI of the brain
   b. General physical exam
   c. Full neurologic exam (by a neurologist)
   d. Brief physical function questionnaire
   e. Cognitive testing (e.g. brief screening questionnaire, more quantitative assessments, etc)
   f. JC virus assay in serum and/or cerebrospinal fluid

8. Based on currently available efficacy and safety data, should Tysabri be approved for the treatment of Crohn's disease, assuming that an effective risk management plan is in place? Specify for which CD patient population Tysabri should be indicated.