FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

HILTON WASHINGTON DC/ROCKVILLE
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QUESTIONS TO THE ADVISORY COMMITTEE

JANUARY 7 & 8, 2009

For January 7, 2009: For treatment of refractory complex partial seizures in adults

1. Vigabatrin has been shown to cause irreversible visual loss (central and/or peripheral).
    a. Does the committee believe that continued treatment results in a clinically meaningful loss of vision in some patients?
    b. Has the sponsor shown that this visual loss can be detected before it becomes clinically meaningful?
    c. Has the sponsor adequately shown that discontinuation of treatment halts the progression of the visual loss?
    d. The sponsor asserts that vigabatrin does not cause central visual loss. Does the committee think that the sponsor has adequately shown this?

2. Can the committee envision any combination of patient population and conditions of use that would support approval?

3. If yes to question 2, then:
    a. What is the appropriate population (e.g., standard population of patients with epilepsy or some subset [e.g., candidates for surgery or intractable patients who are not surgical patients])?
    b. If Sabril is to be approved for use in a refractory population, should additional effectiveness (comparative) data be obtained specifically in this population?

4. If yes to question 2, under what circumstances could Sabril be approved? For example, should it be available only under a Risk Evaluations and Mitigation Strategy (REMS)?

    Following is a partial list of potential components of a REMS:
    -Should it be made available only under restricted conditions (e.g., certain practitioners, restricted distribution, an educational campaign, special training program for practitioners, registry, etc.)?
    -Should continued access to the drug be linked to results of ophthalmologic monitoring?

-Other?

5. Is there sufficient evidence to support specific recommendations on the schedule of ophthalmologic monitoring?
    a. Should there be a requirement for periodic ophthalmologic monitoring?
    b. If so, is the sponsor's plan for monitoring adequate?
    c. If the sponsor's plan is not adequate, does the committee have any proposal?

6. Is there additional data related to the visual loss that should be obtained prior to approval of Sabril? If yes, what data?

7. Does the Committee believe that the intramyelinic edema seen in animals has any clinical consequences in adults?

8. If yes to number 7, should there be additional clinical requirements (e.g., additional monitoring, additional analyses, additional data)?

9. Given the data in hand, does the committee recommend that Sabril should be approved for the treatment of partial seizures?

For January 8, 2009: For treatment of infantile spasms

1. Has the sponsor provided substantial evidence for vigabatrin as a treatment of infantile spasms?

2. Do the studies indicate efficacy in: 1) cessation of spasms, 2) amelioration of the EEG, 3) prevention of other seizures types later in life, or 4) improvement in long-term developmental outcome?

3. There is a view that current unapproved treatments (ACTH or steroids) can provide long-term protection against infantile spasms with a short duration course of treatment (e.g., about two weeks). The sponsor has proposed that vigabatrin be given chronically but has not provided evidence from controlled trials that treatment with vigabatrin chronically provides an additional benefit beyond a brief treatment course. Should the sponsor be required to adequately study this question?

4. Vigabatrin has been shown to cause irreversible visual damage, and the sponsor has proposed that monitoring with ERG can adequately detect this damage at an acceptably early stage.

    a. Has the sponsor provided evidence that ERG is a reliable way to detect lesions in the pediatric population before they become clinically meaningful?

b. Has the sponsor presented any other methods to detect lesions sufficiently early?
c. If the committee concludes that the sponsor has identified an adequate method to detect visual damage sufficiently early, is there evidence to support a monitoring regimen over time that will detect damage sufficiently early? If there is inadequate evidence to support a monitoring regimen, should the sponsor be required to develop that evidence?
d. If the committee concludes that the sponsor has not identified an adequate method to detect damage sufficiently early, should the sponsor be required to develop one?
e. Has the sponsor adequately shown that the visual loss will not progress if the treatment is discontinued once visual damage has been detected?
f. Has the sponsor provided adequate evidence about the functional consequences of treatment with vigabatrin on the developing visual system and overall function, especially against the background of preexisting neurological abnormalities?

5. Has the sponsor presented adequate evidence that central visual loss does not occur in pediatric patients?

6. Can the committee envision any combination of patient population and conditions of use that would support approval?

7. If yes to question 6, then:
   a. What is the appropriate population (e.g., all patients with infantile spasms, only age-specific subsets, etiologic subsets such as tuberous sclerosis, patients who have failed other treatments)?
   b. If Sabril is to be approved for use in a specific subset of patients, should additional effectiveness data in this subset be obtained?

8. If yes to question 6, under what circumstances could Sabril be approved? For example, should it be available only under a Risk Evaluations and Mitigation Strategy (REMS)?

   Following is a partial list of potential components of a REMS:
   -Should it be made available only under restricted conditions (e.g., certain practitioners, restricted distribution, an educational campaign, special training program for practitioners, registry, etc.)?
   -Should continued access to the drug be linked to results of ophthalmologic monitoring?
   -Other?

9. Given alternative off-label therapy (ACTH, valproic acid etc.), do the safety concerns preclude marketing even if efficacy has been demonstrated?

10. Does the Committee believe that the intramyelinic edema seen in animals has any clinical consequences in pediatric patients?

11. What is the clinical significance, if any, of the observation of neuropil vacuolation in young animals? Are these related to newly appreciated MRI findings in children revealing grey matter lesions? If the committee does not believe that the MRI findings in children are related to the neuropil vacuolation in animals, are they of clinical concern nonetheless?

12. Should additional safety data be obtained prior to approval for Sabril as a treatment for infantile spasms? If so, what data?

13. Given the data in hand, does the committee recommend that Sabril should be approved for infantile spasms?