

Vigabatrin

Risk Evaluation and Mitigation Strategy (REMS)

Peripheral and Central Nervous
System Drugs Advisory Committee

January 7 & 8, 2009

Day 1

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What is a REMS?

- A Risk Evaluation and Mitigation Strategy
 - A risk management plan that utilizes strategies beyond routine labeling to ensure that the benefits of a drug outweigh its risks.
 - Designed to meet specific goals in mitigating product risks
 - FDA has authority to require a REMS

REMS Elements

- A REMS can include
 - Medication Guide for patients
 - Communication plan for healthcare professionals
 - Elements to assure safe use
 - Training or certification of prescribers, dispensers
 - Administration in certain health care settings
 - Documentation of safe use prior to dispensing
 - Required monitoring of patients
 - Enrollment of patients in a registry

When Should a REMS be Considered?

Products should be considered for a REMS if needed to ensure that the benefits of the drug outweigh the risks.

REMS Considerations

- The estimated size of the population likely to use the drug.
- The seriousness of the disease or condition that is to be treated with the drug.
- The expected benefit of the drug with respect to such disease or condition.
- The expected or actual duration of treatment with the drug.
- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.
- Whether the drug is a new molecular entity.

REMS Proposed by Sponsor

- Goals
 - To minimize the risk of Sabril-induced peripheral visual field defect (pVFD) while delivering maximum benefit to the appropriate patient populations
 - To detect Sabril-induced pVFD before it results in clinically meaningful restriction of the patient's peripheral vision
 - To ensure regular ophthalmologic monitoring to facilitate ongoing benefit-risk assessments between physicians and patients/parent or legal guardian

REMS Components Proposed by Sponsor

- Medication Guide
- Communication Plan to communicate risk messages
- Initial prescription by board certified neurologist
- Mandatory prescriber education and attestation of understanding of risk and safety monitoring protocol
 - Physician commits to periodic visual field testing
 - Physician attests to reviewing Medication Guide with patient/parent
- Distribution via specialty pharmacies

REMS Components Proposed by Sponsor

- Patient registry
- After receiving vigabatrin for a short period response is assessed
 - 2-4 weeks for infantile spasms
 - 12 weeks for complex partial seizures
- If response acceptable, prescriber attests that benefits exceed risks & therapy continues
- Mandatory periodic visual field testing for CPS, periodic visual testing reminders for IS

REMS Evaluation Proposed by Sponsor

- Surveys of patients/caretakers and prescribers
- Data from specialty pharmacies
- Compliance with program elements
- Adverse event reporting

Limitations of Sponsor's Proposal

- Assumes fairly safe period of vigabatrin exposure, during which patient response to vigabatrin can be safely evaluated
- Assumes that periodic ophthalmic examinations sufficient to preserve vision
- Intramyelinic edema (IME) risk not mitigated

Can the Risk of VFD be Mitigated by Periodic VF Testing?

- Is there a safe period of exposure?
- Can progression to severe VFD occur in a sudden, unpredictable manner?
- Rational monitoring interval problematic

Can the Risk of VFD be Mitigated by Periodic VF Testing?

- Are there screening tools that can ensure timely accurate assessment of VFDs?
 - Can testing ensure early detection of mild-to-moderate damage?
 - What is the role of repeat testing (needed to increase reliability, but delays diagnosis)?

Can the Risk of IME be Mitigated?

- Sponsor's proposal does not fully address the risk of IME
 - What is the clinical significance of IME?
 - Should risk mitigation for IME be included in the REMS?
- Is periodic monitoring for IME needed?
 - If so, what monitoring protocol should be implemented?
 - Is periodic MRI monitoring practical?

Issue for the Committee

- Can safety monitoring protocols be designed that will mitigate the risks of VFD and IME?
 - What monitoring protocols should be implemented for these risks
 - for children?
 - for adults?