Questions for the Peripheral and Central Nervous System Drugs Advisory Committee on April 28, 1999

AGGRENOX™ (dipyridamole/aspirin) Capsules (NDA 20-884

Boehringer Ingelheim Pharmaceuticals, Inc. is seeking approval of AGGRENOX™, a combination product consisting of extended release dipyridamole 200 mg plus aspirin 25 mg, given twice daily to reduce the combined risk of death and nonfatal stroke in patients who have had transient ischemia of the brain or completed ischemic stroke.

To support effectiveness of AGGRENOX™ for the proposed indication, the sponsor has submitted results of a single multinational clinical trial (ESPS 2). This was a multicenter, randomized, placebo-controlled, parallel groups, factorial design study, involving 7040 patients in Europe. Treatment arms were: dipyridamole 200 mg plus aspirin 25 mg, dipyridamole 200 mg alone, aspirin 25 mg alone and placebo. Study treatment was given twice daily for two years in patients with a history of stroke (defined as completed stroke or TIA). Endpoints assessed were all stroke, all cause death, and the composite endpoint of stroke or death. The protocol is not clear as to which of the endpoints is/are primary.

The study results demonstrate a statistically significant superiority of AGGRENOX™ over dipyridamole alone, aspirin alone, and placebo in preventing stroke. There was no statistically significant difference between AGGRENOX™ and the individual components of the drug on mortality. The result of the composite endpoint analysis needs further discussion because of issues related to the interim analysis, increase in sample size, and multiplicity.

Questions

1. The effectiveness of AGGRENOX™ is being supported by a single European study (ESPS 2). Based on this single study has the sponsor provided substantial evidence of effectiveness of AGGRENOX™ for the desired indication?

2. If no to (1), has the sponsor provided substantial evidence of effectiveness of AGGRENOX™ for any other indication? If so, for what indication?

3. Would you recommend approval of AGGRENOX™ for the requested indication?

4. Would you recommend approval of AGGRENOX™ for an indication other than the requested indication? Is so, for what indication?

5. Are there any particular safety concerns with use of AGGRENOX™?

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