Agenda: Wednesday, April 28, 1999
Peripheral and Central Nervous System Advisory Committee
Issue: Safety and Efficacy of Aggrenox™ (Dipyridamole/aspirin)capsule [NDA 20-884]

8:30 Call to Order, Introductions
Sid Gilman, M.D., Chair, PCNS

Conflict of Interest Statement
Sandra Titus, Ph.D., Executive Secretary, PCNS

Introduction of Issues
Russell Katz, M.D., Acting Director, Neuropharmacological Drug Products

8:40 Presentations by Boehringer Ingelheim Pharmaceuticals Inc.
Introduction
Manfred Haehl, M.D., Senior Vice President, Medical & Drug Regulatory Affairs, BIPI

Stroke Management
Gregory W. Albers, M.D., Associate Professor Neurology,
Director of Stanford Stroke Center, Stanford University

Development Rationale
Thomas Mueller, M.D., Ph.D., Head, Haemostasis Laboratory, Blood Transfusion Center, Oldenburg, Germany

Clinical Findings
James Street, Ph.D., Senior Biostatistician, BIPI

Safety
Kenneth J. Rakowski, M.D., Head, Drug Surveillance and Information, BIPI

Conclusion
Manfred Haehl, M.D., Senior Vice President, Medical & Drug Regulatory Affairs, BIPI

10:10 Break

10:30 FDA Presentations
Overview of NDA
Kathy Robie-Suh, M.D.,Ph.D.,Medical Team Leader, GI and Coagulation Drug Products

Efficacy Issues
Ann Farrell, M.D., Medical Officer. GI and Coagulation Drug Products

Statistical Review
Mushfiqur Rashid, Ph.D., Mathematical Statistician, Division of Biometrics II

12:00 Lunch

1:00 Open Public Hearing

2:00- 5:00 Discussion by Advisory Committee

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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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CENTER FOR DRUG EVALUATION AND RESEARCH

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Speakers for the Open Public Hearing of

Peripheral and Central Nervous System Drugs Advisory Committee

April 28, 1999

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

Dena Van Husen, Senior Vice President, National Stoke Association, Englewood, Colorado

Phillip B. Gorelick, M.D., MPH, Director for the African-American Antiplatelet Stroke Prevention Study in Chicago & Speaker for the National Stroke Association

Mark J. Alberts, M.D, Associcate Professor of Neurology & Director, Stroke Acute Care Unit, Duke University, Durham, North Carolina