



Bristol-Myers Squibb Company

Worldwide Consumer Medicines

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August 1, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Attention: Charles Ganley, MD, Director
Division of OTC Drug Products (HFD-560)
Food and Drug Administration

Re: Docket No. 77N-0094
Internal Analgesic, Antipyretic, and Antirheumatic
Drug Products for Over-the-Counter Use

Request for Feedback Meeting to Discuss Clinical Study Proposal

Dear Dr. Ganley:

The Bristol-Myers Squibb Company (BMS) is requesting a meeting to discuss a proposal to conduct a placebo-controlled clinical trial comparing the effects of the combinations of aspirin (ASA) 500mg/acetaminophen (APAP) 500mg/caffeine 130mg (EES 130) and ASA 500mg/APAP 500mg/ caffeine 65mg (EES 65) with APAP 1000mg alone.

Currently, BMS markets the Excedrin line of over-the-counter (OTC) internal analgesic drug products including Excedrin® Extra Strength (ASA 500mg/APAP 500mg/caffeine 130mg) and Aspirin-Free Excedrin® (APAP 1000mg/caffeine 130mg), which are regulated under the Proposed Rule for Internal Analgesics, Antipyretic and Antirheumatic Drug Products for OTC Human Use.

On July 30, 2001, BMS submitted a Citizen Petition requesting the FDA to reopen the administrative record for the Internal Analgesic/Antipyretic Drug Products rulemaking. Specifically, BMS requested that the Proposed Rule (November 16, 1988, 53 FR 46204) be amended to provide for Category I status

of caffeine as an OTC analgesic adjuvant when combined with APAP alone. In addition, the Petition requested Category I classification of the caffeine 130mg dose when used as an analgesic adjuvant in combination with ASA and APAP or with APAP alone. (In 1995, the Agency recommended that caffeine, for use as an analgesic adjuvant, be limited to 64/65mg per dose.) Further, the Petition included the final clinical study reports for three new, adequate, and well-controlled trials demonstrating caffeine's effectiveness as an analgesic adjuvant in combination with APAP as well as an integrated summary of the evidence supporting caffeine adjuvancy with APAP. In addition, the Petition also included a comprehensive assessment of worldwide caffeine safety data that supports the Category I status of the 130mg dose in combination with ASA and APAP or with APAP alone.

In 1988, BMS submitted (Docket No. 77N-0094, 12/21/88) the results from six well-controlled clinical trials which demonstrated that EES 130 is clinically and statistically superior to APAP 1000, as measured by the standard efficacy measures of total pain relief (TOTPAR) and sum of pain intensity differences from baseline (SPID). Further, there is a long history of clinical and consumer experience with 64mg and 130mg caffeine doses when combined with analgesic bases, however there are no adequate and well-controlled clinical trials that have directly compared the analgesic adjuvancy of the 130mg dose versus 65mg of caffeine. To address this matter as well as the request in the Agency's April 13, 2001 letter for information demonstrating the incremental benefit of the caffeine 130mg dose versus 65mg, BMS is proposing to conduct a placebo-controlled clinical trial comparing the effects of the combinations of EES 130 and EES 65 with APAP 1000mg alone. A positive dose response in this trial would provide convincing evidence for increased analgesic adjuvancy with increased caffeine dose and provide information on the dose-response relationship between EES 130, EES 65, and APAP 1000mg. BMS is also proposing that the results from this clinical study be extrapolated to support the combination of APAP 1000mg/caffeine 130mg.

Our objective is to obtain the Agency's feedback on the adequacy of the attached clinical trial proposal. In addition, BMS seeks Agency concurrence that the availability of positive results from the clinical trial in conjunction with the comprehensive safety assessment for caffeine provided in our Citizen Petition (Docket No. 77N-094, 7/30/01) will satisfy requirements in support of Category I classification of the caffeine 130mg dose as an analgesic adjuvant. BMS is requesting that the Agency provide a stay in the finalization of the Internal Analgesic Monograph relative to the caffeine 130mg dose until the results of the proposed clinical trial are submitted and reviewed by the Agency.

The following is a list of anticipated individuals representing BMS Worldwide Consumer Medicines:

- Jorge Insuasty, MD – Executive Medical Director, Medical & Clinical Affairs
- Howard Hoffman, MD – Executive Medical Director, Clinical Research
- Jeffrey Baggish, MD – Medical Director, Clinical Research
- Rich Cuprys – Director, Regulatory Affairs
- Jean Battikha – Sr. Manager, Statistics and Data Management
- Eugene Laska, Ph.D – Consultant

We request that the following Agency personnel attend the meeting:

- Charles Ganley, MD – Director (HFD-560)
- Linda Katz, MD – Deputy Director (HFD-560)
- Walter Ellenberg, Ph.D – Project Manager (HFD-560)

We would be available to meet at a mutually convenient time after September 4, 2001.

If you have any questions or comments regarding this submission please contact me at (908) 851-6126.

Sincerely,



Rich Cuprys
Director, Regulatory Affairs
Bristol-Myers Squibb Company
Worldwide Consumer Medicines
1350 Liberty Avenue
Hillside, NJ 07205

CC: Walt Ellenberg, Ph.D. (HFD-560)