DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

1037 '02 FEB -7 A9:17

FEB 5 2002

Richard Cuprys, R.Ph.
Director, Regulatory Affairs
Bristol-Myers Squibb Company
1350 Liberty Avenue
Hillside, New Jersey 07205

Re: Docket No. 77N-0094
CP 15

Dear Mr. Cuprys:

This letter is in response to your submission dated August 1, 2001 requesting a meeting to discuss your proposed protocol to demonstrate an incremental benefit of 130 mg caffeine over 65 mg caffeine for use as an Over-the-Counter analgesic adjuvant.

The Agency has reviewed your protocol outline entitled: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Single-Dose Study Comparing the Efficacy of Two Different Formulations of Excedrine Extra Strength with Extra Strength Tylenol and Placebo in the Acute Treatment of Episodic Tension-Type Headache and has the following comments.

The agency does not believe that a meeting is warranted at this time until major revisions to the design of the study are made. Once these changes are made, a complete protocol rather than a protocol outline should be submitted for review. The agency would then consider meeting to discuss unresolved issues. The agency offers these comments on the protocol outline.

1. For the purpose of establishing the caffeine dose response, the comparison of efficacy between the aspirin/acetaminophen/caffeine (AAC) combinations and acetaminophen 1000 mg is not very informative. The primary objective of the study should be the evaluation of the relative efficacy of the AAC combinations to placebo and with each other.

2. To fully assess the adjuvancy of caffeine, the study should include an aspirin 500 mg /acetaminophen 500 mg arm to assist in the assessment of the dose response relationship between aspirin 500 mg /acetaminophen 500 mg /caffeine 65 mg and aspirin 500 mg /acetaminophen 500 mg /caffeine 130 mg.

3. It is not clear that the results from a headache study can be used to support the other general claims available for internal analgesics. Caffeine may have unique benefits in a headache model that may not be apparent in other pain models (e.g. dental pain models). For this reason, the agency recommends that another model be used to assess the dose response for caffeine as an adjuvant.

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4. The primary endpoints and primary comparisons are not clearly stated in the outline.

5. For an acute analgesic claim, a drug should work within 1 hour of ingestion. The proposed protocol as currently designed to assess one designated "summary" primary efficacy parameter at 4 hours (i.e., TOTPAR4). TOTPAR4 is not an acceptable primary efficacy variable. Single-dose analgesic trials are traditionally designed to evaluate multiple primary efficacy parameters that are directly generated from assessments made during the trial by the subjects. Therefore, you should use other primary efficacy variables such as pain intensity (PI) and pain relief (PR) that need to be evaluated every 20 minutes or the first 2 hours and then at 3 hours post dosing in addition to the other parameters that you are proposing to study (i.e., time to onset of meaningful pain relief, time to rescue medication, etc...).

6. The statistical analysis section of the protocol should provide more details of the planned analyses and the order in which they are conducted. The protocol should describe how subjects who use rescue medications are incorporated into the analysis.

7. In order to demonstrate a desired treatment effect in analgesic trials, the sample size of the treatment groups is traditionally 50 subjects per study arm in single ingredient studies. Combination products usually contain 80-90 subjects per study arm. Please explain why 400 subjects per arm are needed.

8. Clarify the rescue medication that will be used in those subjects who fail to respond to study medication.

9. Please clarify how you intend study subjects to evaluate the "other measures' listed in the protocol under efficacy evaluations such as muscle stiffness, psychic tension, degree of relaxation, and interference with daily activities. Information regarding the parameters and methods validation should also be provided.

10. The 2-stopwatch method is a better method than the 1-stopwatch method to measure the onset of pain relief since it provides information to calculate the time to perceptible pain relief and the time to meaningful relief.

11. Please clarify the method by which you intend to analyze the safety data collected during the study.

12. Please collect information from subjects regarding their previous use of OTC analgesics (i.e. type of products used, frequency of use, benefit).

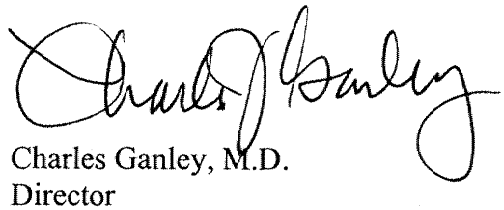
13. Adverse event information should be archived by the subjects in their diaries.

14. Please include a copy of the consent form and sample diary card with the revised protocol.

15. The agency has not had an opportunity to review the safety information for combination products containing 130 mg of caffeine. This information was included in the citizen petition. Consequently, we have no comments on the safety of this combination at this time.

The Agency would be available for a teleconference to clarify any questions generated from the comments regarding the protocol outline. Should you desire such a teleconference or have further questions, please contact Walt Ellenberg, Ph.D. at 301-827-2241.

Sincerely yours,



Charles Ganley, M.D.
Director
Division of OTC Drug Products
Center for Drug Evaluation V
Food and Drug Administration

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2-1-02

FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 77N-0094

TO: Dockets Management Branch, HFA-305

☒ The attached material should be placed on public display under the above referenced Docket No.

☐ This material should be cross-referenced to Comment No. _____

Charles J. Ganley, M.D.

Attachment