



FEB 24 2006

Consumer Healthcare Products Association  
Attention: Lorna C. Totman, Ph.D.  
Acting Vice President, Regulatory and Scientific Affairs  
900 19<sup>th</sup> Street, NW, Suite 700  
Washington DC 20006

Re: Docket No. 1981N-0033  
Comment No: C76

Dear Dr. Totman;

This letter responds to your submission dated December 20, 2004, of a revised protocol, BZ-03-07, Benzocaine Gel Toothache Dose-Response Study. The submission is coded as C76 in Docket No. 1981N-0033 in the Division of Dockets Management.

The study is a randomized, double-blind, placebo-controlled trial to evaluate the effectiveness of 10% and 20% benzocaine in relieving toothache pain. Benzocaine is currently classified as Category III for toothache relief (insufficient effectiveness data) in the Tentative Final Monograph for OTC Oral Health Care Drug Products (56 FR 48302, September 24, 1991). The proposed study is intended to support a Category I (safe and effective) classification for benzocaine for this indication.

The proposed study provides a generally suitable venue and protocol for assessing the product's efficacy in the intended population. However, several aspects related to data collection and analysis could limit or preclude a meaningful benefit-risk analysis and impact product labeling. We have the following comments and recommendations:

The following items (1 through 10) pertain to collection and analysis of efficacy data, assessment in the proposed protocol. Safety issues are addressed in items 11 and 12.

1. Analyses of the Dental Pain Scale (DPS) data have been proposed as your primary efficacy endpoint. While DPS is recognized as a validated metric, we recommend that you consider the use of a visual analog scale (VAS) score for pain assessment throughout the trial (in addition to the proposed baseline assessment). VAS has been more widely validated and may provide a more precise measure, particularly of the onset and duration of pain relief. If both DPS and VAS metrics are employed, you should identify a priori, the specific analyses of each metric that will serve as primary and secondary endpoints.

2. A clinically and statistically significant difference between active and placebo treatments will be required of the primary endpoint to support efficacy, for each strength. The magnitude of a clinically significant difference between active and placebo treatments must be defined in the protocol and the definition must be supported by data. We recommend that for trials of pain medication, the assessment of onset, duration, and magnitude of pain relief be compared to the outcome of a global satisfaction assessment as a means of demonstrating clinically significant differences between treatments.
3. As proposed, a difference of 5 percent in the number of responders between the 10 and 20 percent strength benzocaine active treatment groups on the DPS would be considered clinically significant, whether it occurs across the entire population or only within the subgroup of patients presenting with severe toothache at baseline. The definition of a clinically significant difference (e.g., the proposed 5 percent difference) should be supported by data.
4. A secondary endpoint would be expected to show a trend supporting the primary endpoint outcome for us to make a determination of efficacy for each of the active treatments compared to placebo. Likewise, the existence of a dose response relationship between active treatment strengths would need to be supported with similar findings between the primary and secondary endpoints.
5. A two-stopwatch technique for determining onset of meaningful relief should be used, as discussed at the June 3, 2002, meeting.
6. Instructions for uniform selection and dosing of rescue medications should be included in the protocol for both pediatric and adult subjects.
7. Pain relief combined with pain intensity difference score (PRID) was not clearly defined. Verification should be provided to indicate that it is the "pain relief intensity difference," calculated by adding the Pain Intensity Differences (PID) and Dental Pain Relief Scale (DPRS) scores at each post-dosing time point.
8. The means of weighting the sum of pain relief combined with pain intensity difference (SPRID) scores by time was not specified.
9. Regarding secondary efficacy parameter #3 (SPRID scores over 30, 60, 90, 120 minutes) and parameter #4 (pain relief combined with PRID at each measurement time): by including the four testing periods for parameter #3 (30, 60, 90 and 120 minutes) and 15 testing periods for parameter #4, there are total of 22 separate comparisons for secondary endpoints. This raises the problem of multiple comparisons and needs correction or reduction of the number of variables.

10. The protocol should be written to specify who should measure the dose, particularly for children (age 12 and older).

The study does not address the following issues which are essential for establishing safety of the drug product.

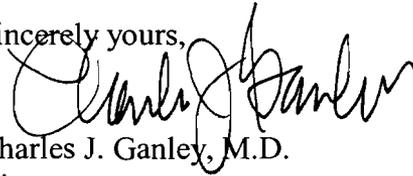
11. Subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency and severe respiratory problems that are likely to be adversely affected by methemoglobinemia should be excluded from the trials.
12. Subject safety should be proactively assessed at regular intervals during the 2-hour observation period. These evaluations should include vital sign measurements, as well as assessments of level of wakefulness and symptoms associated with local anesthetic toxicity such as light headedness, paresthesias, and nausea. The protocol should provide a plan for management of patients who appears to be experiencing distress.

We recommend that you submit the final protocol to us for review 30 days prior to initiating the study.

If you have any comments or questions regarding these recommendations, please reference the docket and comment numbers at the beginning of this letter and submit them to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

We hope this information is helpful.

Sincerely yours,



Charles J. Ganley, M.D.

Director

Office of Nonprescription Products

Center for Drug Evaluation and Research