DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED BY FACSIMILE

March 13, 1998

Howard Pien
President, North America
SmithKline Beecham Pharmaceuticals
One Franklin Plaza
Philadelphia, PA 19102

Re: NDA 19-583
Relafen (nabumetone) Tablets
MACMIS #5666

WARNING LETTER

Dear Mr. Pien:

This Warning Letter addresses SmithKline Beecham Pharmaceutical's (SB) dissemination of promotional materials concerning Relafen (nabumetone) Tablets. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed these materials as part of its monitoring and surveillance program. DDMAC has concluded that SB, in its promotion of this product, has disseminated materials that contain statements or suggestions that are false or misleading in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. §§ 352(a) and 331(a) and regulations promulgated thereunder (see 21 C.F.R. §§ 201.1(e)(6)(I), (ii), (vii)).[1]

Relafen is a nonsteroidal anti-inflammatory drug (NSAID) that is approved for acute and chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis. The promotional materials in question present selected data from nonclinical, *in vitro* studies to suggest clinical significance when no clinical benefit has been established. Additionally, SB presents data that imply that Relafen is superior to other nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of such superiority from adequate and well-controlled clinical studies.

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[1] These materials include, but are not limited to, brochures RL4518, RL8137, RL4322, RL4369, RL8711, posters RE 961 TB and RE 962 C, and a reprint article by Lapin and Poland, "Clinical Update of the Relative Safety of Nabumetone in Long-term Clinical Trials," Inflammopharmacology 1995; 3:351-361.

I. Background

As with other NSAIDs, Relafen's mode of action is unknown. However, it is believed that the ability to inhibit prostaglandin synthesis may be involved in its anti-inflammatory effect.

Prostaglandins are formed by the action of the enzyme cyclooxygenase (COX) on arachidonic acid. Prostaglandins play an important role in gastric mucosal, renal, and platelet function. Prostaglandins are also important contributors to the signs and symptoms of inflammation. Recently two forms of COX have been identified, COX-1 and COX-2. COX-1 is found in a number of tissues and is believed responsible for the homeostatic and protective actions of prostaglandins listed above. It is hypothesized that inhibition of COX-1 results in many of the adverse events associated with the use of NSAIDs.[2]

In contrast, COX-2 is not found in the normal resting condition but is found in response to inflammatory stimuli and is responsible for the enhanced production of arachidonic acid metabolites at sites of inflammation.[3] Thus, it has been hypothesized that inhibition of COX-2 results in anti-inflammatory and analgesic effects. It is hoped that an anti-inflammatory agent that selectively inhibits COX-2, but does not inhibit COX-1 would be able to treat the signs and symptoms of inflammation without causing the type of adverse events associated with the use of NSAIDs. This hypothesis is, however, not yet established and the manufacturers developing COX-2 selective agents have been asked to support such advantages with clinical data before making such claims.

II. SB's Promotional Claims for Relafen

SB's promotional claims for Relafen lack adequate substantiation in at least five aspects, and thus are false or misleading. First, SB presents results from *in vitro* studies that used cell cultures to determine the selectivity profiles for COX-2 vs. COX-1 for Relafen and other NSAIDs to suggest clinical superiority for Relafen. In fact, these studies demonstrated no such clinical superiority.

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2 Peter E. Lipsky, MD, address entitled "Progress Toward a New Class of Therapeutics: Selective COX-2 Inhibition" at a symposium sponsored by Southwestern Medical Center (October 22, 1996).

3 Id.

Second, SB claims that there are fewer peptic ulcers associated with the use of Relafen than with other NSAIDs. However, these safety claims were based on inadequate data and are not supported by evidence from adequate and well-controlled, head-to-head clinical trials.

Third, SB claims that Relafen has no significant effect on platelet aggregation. These claims were not substantiated by adequate platelet aggregation or bleeding time studies.

Fourth, SB claims that Relafen has no significant effect on renal function. These claims were not substantiated by adequate renal function tests. Therefore, FDA considers these promotional claims suggesting or implying Relafen is superior to other NSAIDs false or misleading.

Finally, SB combines the *in vitro* study purportedly demonstrating Relafen to be COX-2 selective with results from clinical studies and reprint articles allegedly demonstrating Relafen's minimal GI adverse events, lack of effect on platelet aggregation, and lack of significant effect on renal function to suggest that Relafen is COX-2 selective, and thus, superior to other NSAIDs. In the absence of adequate clinical data necessary to substantiate these claims and implications, dissemination of promotional materials containing these types of claims are violative of the Act. Each of these issues is discussed in greater detail below.

Moreover, in a letter from DDMAC dated January 23, 1997, SB was informed that its claims of COX-2 selectivity and superiority to other NSAIDs based on data from nonclinical studies were false or misleading in violation of the Act. Nevertheless, SB continues to disseminate materials containing these claims.

A. Use of Nonclinical Data (Cyclooxygenase Selectivity)

As part of its effort to claim that Relafen is COX-2 selective, SB disseminated a promotional card.[4] One side of the card presents a graphic describing the purported roles of COX-1 in the maintenance of the gastric mucosa, maintenance of normal renal function, and platelet aggregation, and of COX-2 in the inflammatory process. The other side of the card presents the results of *in vitro* cell culture studies that compare the selectivity of Relafen and other NSAIDs for COX-2 vs COX-1 activity, combined with statements that Relafen "exhibits greater selectivity for COX-2 than COX-1." This presentation of the purported roles of COX-1 and COX-2 combined with statements and bar charts that represent the *in vitro* selectivity of inhibition of COX-1 and COX-2 for various NSAIDs, suggests that the information has clinical significance and that Relafen is superior to other NSAIDs.

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[4] This brochure is a two-sided card identified as RL4518.

SB has not submitted evidence that demonstrates that the purported "COX-2 selectivity" of Relafen has clinical significance. Moreover, Relafen has not been shown to be clinically superior, with respect to either efficacy or safety, to other NSAIDs in adequate, well-controlled, head-to-head clinical trials. Thus, SB's stated and implied claims that Relafen is COX-2 selective and therefore, less toxic than other NSAIDs is false or misleading.

In its January 23, 1997, letter, DDMAC advised SB that it had not provided adequate substantiation to support its promotional claims that Relafen is COX-2 selective and clinically superior or less toxic to the GI tract than other NSAIDs. In its response dated February 7, 1997, SB advised the Agency that the use of promotional materials that contained the violative claim relating to COX-2 selectivity had been discontinued. The agency is seriously concerned about this repetitive conduct.

B. Superiority Claims

1. Gastrointestinal Tolerability

As part of its promotional campaign to claim that Relafen is COX-2 selective, SB includes claims that Relafen has fewer gastrointestinal adverse events than other competitive NSAIDs. In its promotional brochures,[5] SB presents a graphic to claim that Relafen has a significantly lower cumulative incidence of "perforations, ulcers, and bleeds" (PUBs) than other NSAIDs. This graphic presentation is based on pooled data from post-marketing studies that evaluated the efficacy and safety of six NSAIDs individually. SB then combined the safety data for each of the other six NSAIDs from these individual studies to derive a combined incidence of GI adverse events for "other NSAIDs." SB compared this composite figure to the incidence of adverse events for Relafen derived from clinical studies evaluating the safety and efficacy of Relafen. The use of these studies in this manner is misleading in that these individual studies were not designed for comparative purposes, and the retrospective meta-analysis to derive a composite GI adverse event incidence for "other NSAIDs" cannot be used for comparative promotional claims. DDMAC considers these cross-study comparative claims to be false or misleading. Differences between the studies with respect to such variables as study population, doses of drugs, quality of evaluations, and timing of dosing and of evaluations could easily lead to different rates of PUBs that are not the consequence of different effects of the drugs.

Additionally, SB claims that Relafen is "the gold standard for GI safety." This claim implies that Relafen is known to be superior to all other NSAIDs concerning GI tolerability. However, SB

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[5] These materials include, but are not limited to, brochure RL5572, RL4322 and RL4369.

has not demonstrated by substantial evidence from adequate, well-controlled, head-to-head clinical trials that the ulcer rate with Relafen is lower than that observed with any other NSAID, much less all other NSAIDs. Nor has SB submitted data in support of its claim that Relafen is clinically and statistically significantly less ulcerogenic than other NSAIDs.

In a letter dated July 31, 1997, in response to DDMAC's request for substantiation of these promotional claims concerning GI tolerability for Relafen, SB cited data previously submitted as support for these promotional claims. These data have been reviewed and were not considered adequate to support SB's claims. Moreover, such claims are not consistent with, and tend to undermine, the warnings and other risk information in SB's approved product labeling for Relafen. The Warnings section of the approved product labeling for Relafen, like all NSAIDs, states that "serious gastrointestinal toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy." Thus, it is false or misleading to suggest or imply that Relafen is superior to other NSAIDs concerning its potential GI toxicity.

Similarly, SB claims that Relafen reduces the risk of NSAID-induced GI injury because the chemical compound, nabumetone, is nonacidic and hydrophobic. SB compares the nonacidic characteristics of Relafen with other NSAIDs that SB states have a direct topical effect through concentration in gastric mucosa. SB suggests that because of Relafen's physico-chemical characteristics there may be no active drug exposure to the gastric mucosa, resulting in a superior GI safety profile. However, as noted previously, SB has not provided evidence from adequate and well-controlled studies to demonstrate that Relafen has a GI safety profile superior to other NSAIDs. Claims that Relafen is superior to other NSAIDs because of its nonacidic hydrophobic nature, without clinical evidence of such superiority, are false or misleading.

2. Hemostasis and Platelet Aggregation

The second component of its effort to claim that Relafen is COX-2 selective is SB's promotional materials[6] that state that Relafen has "no effect on bleeding time," that Relafen "reduces the risk of GI bleeding," and that "haemostasis is unaffected" by the use of Relafen.

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[6] These materials include, but are not limited to, posters RE 961 TB and RE 962C, brochure RL8711, and a reprint article by Lipani and Poland, "Clinical Update of the Relative Safety of Nabumetone in Long-term Clinical Trials," Inflammopharmacology 1995; 3:351-361.

SB cited two studies (Freed et al. and Balla et al.)[7] in support of its claim concerning the lack of effect on bleeding time and hemostasis. These references do not support SB's claim. Freed et al. conducted a three-way complete crossover, seven-day study of nabumetone, indomethacin, and sulindac in 14 healthy female volunteers evaluating bleeding time and platelet aggregation. The authors reported that three of the 14 subjects had clinically significant abnormal bleeding times of greater than 15 minutes while receiving Relafen. These data suggest that Relafen does have an effect on bleeding time. Balla et al. conducted an open-label study of 26 healthy volunteers who received Relafen 1000 mg once-daily. The authors reported no significant changes in group mean bleeding times, but the bleeding times could not be adequately assessed without examining individual data. Accordingly, SB's claims concerning hemostasis and platelet aggregation are false or misleading because the evidence submitted does not support them.

3. Renal Function

The third component of its effort to claim that Relafen is COX-2 selective involved SB's claims that Relafen demonstrated "no significant effect on renal function in patients at high risk of renal compromise."[8] To support this claim, SB referred to a study by Cook et al.[9] that evaluated 17 female patients in a triple-cross over trial with 1 month treatment of nabumetone, sulindac, and ibuprofen. This small study was inadequately powered and does not support SB's safety claims concerning Relafen. Moreover, this promotional claim is inconsistent with the approved product labeling for Relafen, which states in the "Precautions" section that "as with all NSAIDs. patients with impaired renal function should be monitored more closely than patients with normal renal function." SB's statement that there is no significant effect on renal function with Relafen potentially puts patients at risk and is false or misleading.

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7 Freed MI, Audet PR, Zariffa N, et al., Comparative effects of nabumetone, sulindac, and indomethacin on urinary prostaglandin excretion and platelet function in volunteers. *J Clin Pharmacol.* 1994; 34:1098-1108.

Al Balla S, et al., Interaction between nabumetone--a new non-steroidal anti-inflammatory drug--and the haemostatic system ex vivo. *Haemostasis.* 1990; 20:270-275.

8 These materials include, but are not limited to, brochure IH8137 and RL4322.

9 Cook ME, Wallin JD, Thakur VD, et al., Comparative effects of nabumetone, sulindac and ibuprofen on renal function. In press.

III. Conclusions and Requested Actions

SB's activities have resulted in the dissemination of false and misleading information about its drug Relafen. Accordingly, SB should propose an action plan that includes the mailing and publication of a "Dear Healthcare Professional" letter, in order to disseminate corrective messages about the issues discussed in this letter. This letter should be provided to all health care providers, institutions, and organizations who received the violative messages.

This action plan should also include:

A. The immediate cessation of dissemination of all promotional activities and materials: (1) that state, suggest, or imply that Relafen is COX-2 selective or is superior to other NSAIDs or, (2) that contain false or misleading claims of the type discussed in this letter.

B. A written statement of SB's intent to comply with "A" above.

C. The dissemination, within 15 days of the date of this letter, of a message to all SB sales representatives and marketing personnel involved in the marketing and sales of Relafen, instructing them to immediately cease dissemination of all promotional materials and messages discussed in this letter, and providing each person with a copy of this letter.

Because of the scope of SB's violative promotional campaign, the Dear Healthcare Professional letter and SB's action plan should be submitted to DDMAC for approval. After such approval, the letter should be disseminated by both direct mail and through a paid advertisement in all journals that contained advertisements for Relafen during the 12 months prior to the date of this letter.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of SB's campaign for Relafen and we may determine that additional remedial measures will be necessary to fully correct the false or misleading messages resulting from SB's violative conduct.

If SB has any questions or comments, please contact Stephen Sherman, Thomas Abrams, or Norman Drezin by facsimile at (301) 594-6771, or at the Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, Maryland 20857. DDMAC reminds SB that only written communications are considered official.

In all future correspondence regarding this matter, please refer to both the NDA number and the MACMIS ID #5666.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

Minnie Baylor-Henry

Minnie Baylor-Henry, R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising, and Communications