DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

FDA

Food and Drug Administration
Rockville MD 20857

JAN 23 1997

TRANSMITTED BY FACSIMILE

Richard Swenson, Ph.D.
Associate Director, U.S. Regulatory Affairs
SmithKline Beecham Pharmaceuticals
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426-0889

Re: NDA 19-583
Relafen (nabumetone) Tablets
MACMIS ID #4877

Dear Dr. Swenson:

This letter is in reference to SmithKline Beecham Pharmaceutical's (SB) submissions of promotional materials under cover of FDA Form 2253 for Relafen (nabumetone) Tablets. These materials consist of promotional brochures and reprint articles. The Division of Drug Marketing, Advertising, and Communications (DDMAC) regards these brochures[1] and reprint articles[2] to be false and/or misleading under the Federal Food, Drug, and Cosmetic Act and regulations promulgated thereunder.

1. Use of Nonclinical Data (Cyclooxygenase Selectivity)

Specifically, DDMAC contends that SB has presented data from nonclinical studies of nabumetone in such a way that suggests they have clinical significance, when in fact no such

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[1] These brochures include, but are not limited to RL8711 and RL9299.

[2] These reprint articles include:

A. Roth, SH: NSAID Gastropathy A New Understanding: *Archives of Internal Medicine* 1996; 156:1623-28.

B. Spangler, RS: Cyclooxygenase 1 and 2 in Rheumatic Disease: Implications for Nonsteroidal Anti-inflammatory Drug Therapy: *Seminars in Arthritis and Rheumatism* 1996; 1:435-46.

clinical significance has been demonstrated. For example, SB presents information concerning the purported roles of cyclooxygenase 1 and 2. These two cyclooxygenase pathways suggest that drugs that are COX-2 selective would provide greater efficacy and tolerability in the treatment of arthritis than drugs that inhibit both COX-1 and COX-2 equally. This implication combined with the presentation of in vitro selectivity for inhibition of COX-1 and COX-2, suggests that nabumetone is superior to many of the other NSAIDs.

The Spanger article contains statements, such as "a pattern emerges in which those NSAIDs exhibiting a preferential action on COX 2 (e.g., nabumetone) are generally less toxic to gastric mucosa than those exhibiting a preferential activity on COX 1" and "convincing data that nabumetone (COX 2-selective) has little effect on renal prostaglandin ..." that suggest nabumetone is superior to other NSAIDs.

However, nabumetone has not been shown to be clinical superior to other NSAIDs in head-to-head clinical trials. SB's proposed cyclooxygenase pathway as the mechanism of action for nabumetone is also inconsistent with the approved product labeling. The approved labeling states that:

> As with other nonsteroidal anti-inflammatory agents, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect.

Although it is known that NSAIDs inhibit cyclooxygenase, it is unknown to what degree this mechanism of action accounts for reduction of pain and inflammation associated with their use in the treatment of arthritis. Thus, the information presented in these brochures and reprint article that nabumetone is COX-2 selective and, therefore, less toxic than older NSAIDs is false and/or misleading.

Finally, SB has not submitted substantial evidence that nabumetone is COX-2 selective or "gastrosparing." Without such substantial evidence, suggestions and statements that nabumetone is cyclooxygenase selective and clinically superior or any less toxic to the GI tract than other NSAIDs is false and/or misleading.

2. Cost-Effective Claims

Additionally, unsubstantiated cost-effective claims based on the factors discussed above are also misleading. Thus, the statement in the Roth article that nabumetone has been demonstrated to be cost-effective compared with fixed-combination misoprostol and NSAID is false and/or misleading.

SB should immediately suspend all promotional activities and materials that convey or contain the allegedly violative claims or information identified in this letter. SB should submit a written response to DDMAC on or before February 7, 1997, describing the steps taken to ensure that the use of these materials have been discontinued.

If SB has any questions or comments, pleas contact the undersigned 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 #4877.

Sincerely,

Stephen W Sherman

Stephen W. Sherman, MBA
Regulatory Review Officer
Division of Drug Marketing,
Advertising & Communications

File name: relanov.016

Draft: SSherman - 1/6/97
Comment: TAcker - 1/6/97
Concur: TAbrams - 1/13/97

cc:
HFD-40/NDA 19-583
HFD-40/Chron/Sherman/Abrams
HFD-550/NDA 19-583
HFD-550/LoBiancho

MACMIS File Id #4877
MACMIS Type Code: LETT
MACMIS Action Code: VIOL

Due Date: February 7, 1997
Close Out: **NO**

FOI Status: **RELEASEABLE**