

07 November 2006



GlaxoSmithKline

GlaxoSmithKline
1500 Littleton Road
Parsippany, NJ
07054-3884

Tel. 973 889 2100
Fax. 973 889 2390
www.gsk.com

Andrew Von Eschenbach, M.D., Acting Commissioner
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: *Comments in Opposition to Request for Withdrawal of Xenical from the Market*
(FDA Docket No. 2006P-0154 and 2006P-0154/Sup 1)

Dear Dr. Von Eschenbach,

GlaxoSmithKline Consumer Healthcare (GSK) and Hoffmann-La Roche Inc. (Roche) are writing to express our strong opposition to the citizen petition submitted to the above-referenced docket on April 10, 2006 and supplemented on June 5, 2006 (referred to herein as the "Petition" and "Supplement", respectively).

Roche and GSK, as Sponsors of the approved NDA for Xenical[®] 120mg capsules and the pending application for orlistat OTC, respectively, vigorously refute the scientific premise of the Petition and remain fully convinced of orlistat's safety and efficacy. To-date orlistat has been widely studied in more than 100 controlled clinical trials (including over 30,000 patients), has obtained regulatory approval in 145 countries (including 6 countries where orlistat is non-prescription) and there have been more than 26 million patient treatments worldwide with orlistat since its first approval in 1997.

Attached to this letter are three separate documents that support the Sponsors' joint opposition to the issues raised in the Petition and Supplement.

Background

On April 10, 2006, Public Citizen filed a citizen petition (Docket No. 2006P-0154/CP 1) to the United States Food and Drug Administration requesting that FDA take immediate action to remove Xenical[®] (orlistat) Capsules, 120 mg from the US market. The petition further states that FDA should not approve GlaxoSmithKline's pending new drug application for the use of orlistat 60 mg capsules as an over-the-counter weight loss aid (Alli[™] orlistat 60 mg Capsules). The basis of Public Citizen's

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recommendation is the observation of increased aberrant crypt foci (ACF) in some preclinical studies with orlistat and scientific literature discussing the potential link between the development of colon cancer and ACF. GSK and Roche (collectively referred to as the "Sponsors") do not agree with the conclusions or the scientific rationale for the conclusions put forth in the Petition and Supplement.

In order to address the issues raised in the Petition and Supplement, which Roche and GSK take very seriously, the Sponsors have re-reviewed all the relevant preclinical, clinical and post-marketing data for orlistat, including the ACF data, to assess the potential risk of developing colon cancer as a result of orlistat therapy. In addition, a review of epidemiology data was also conducted to identify risk factors for colorectal cancer in humans. This data review was based on the current body of preclinical, clinical and post-marketing safety data.

The Sponsors' assessment of the scientific issues, which reflects the combined scientific opinion of GSK and Roche, is provided in three documents designated as Attachments 1, 2 and 3 respectively.

- Attachment 1 is a point-by-point assessment of overall general issues raised in the Petition and Supplement.
- Attachment 2 is a detailed summary of the orlistat preclinical and clinical data and colon cancer. Attachment 2 addresses both the data referenced by Public Citizen in their Petition and includes additional preclinical and clinical data not discussed in the Petition.
- Attachment 3 is the report of an independent expert task force meeting (referred to herein as the "Colon Scientific Advisory Board") who reviewed the relevant preclinical and clinical orlistat data and concluded that there is no evidence that orlistat increases the risk of colon cancer in humans.

As previously mentioned the primary basis of the Petition is the observation of increased aberrant crypt foci (ACF) in some preclinical studies with orlistat and scientific literature discussing the potential link between ACF and the development of colon cancer. It is important to note that ACF is not a validated biomarker for colon cancer and the observation of increased ACF in rodent models is not new. The observation, and the clinical relevance thereof, has been thoroughly evaluated as part of the comprehensive development program for Xenical®. This program included early exploratory studies such as short-term rodent studies as well as long-term carcinogenicity studies in animals and human clinical data. The results of these key

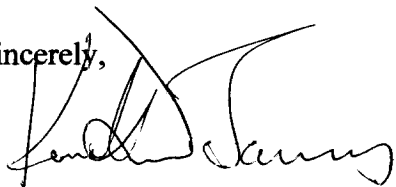
studies and the current body of data confirm the safety of orlistat and provide firm evidence there is no association between colon cancer and orlistat.

To provide an objective analysis of the current body of preclinical and clinical data in the context of current medical science, an independent panel of internationally recognized experts in the fields of cancer research, gastroenterology, toxicology and obesity was convened to review the orlistat data and determine orlistat's colon safety. This Colon Scientific Advisory Board has independently concluded that there is no evidence that orlistat increases the risk of colon cancer in humans (Attachment 3). The present conclusions are entirely consistent with FDA's current findings of orlistat's safety and efficacy.

Additionally, the Sponsors do not agree with the Petition's request that FDA not approve the pending new drug application for the use of orlistat 60 mg capsules as an over-the-counter weight loss aid which is currently under review by the Agency. GSK considers that the comprehensive body of safety and efficacy data for orlistat firmly supports the proposed OTC use of the drug.

In summary the Sponsors remain fully confident of the safety and efficacy of orlistat for weight loss and weight management. Further, we remain convinced that millions of Americans need a safe and effective therapeutic option to help them lose weight. Orlistat capsules (Rx and OTC versions) can have a significant role in addressing the public health crisis of overweight and obesity in this country. For these reasons we believe that the Petition and Supplement should be denied. We further believe that no change in the marketing status or labeling of orlistat Rx is warranted and there should be no delay in the approval and subsequent marketing of 60mg orlistat as an OTC product.

Sincerely,



Kenneth W. James
Senior Vice President
Research and Development
GlaxoSmithKline Consumer Healthcare

Attachment 1 Summary of Comments in Opposition to Public Citizen's Petition
Requesting Withdrawal of Prescription Xenical from the Market and

**the Rejection of Approval of Orlistat Capsules for Over-the-Counter
Use (FDA Docket No. 2006P-0154 and 2006P-0154/Sup 1)**

Attachment 2 Orlistat Preclinical and Clinical Summary Report on Colon Cancer

Attachment 3 Summary of Colon Scientific Advisory Board



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Food and Drug Administration
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Lars Birgerson, M.D., Ph.D.
Vice President, Medical Affairs



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Hoffmann-La Roche Inc.

Sincerely,

A handwritten signature in black ink, appearing to read "Lars Birgerson".

Lars Birgerson, M.D., Ph.D.
Vice President, US Medical Affairs

Lars Birgerson, M.D., Ph.D.
Vice President, Medical Affairs



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