



NDA 20766/S-028

SUPPLEMENT APPROVAL

Hoffmann-La Roche, Inc.
Attention: Margaret J. Jack
Program Director
340 Kingsland Street
Nutley, NJ 07110-1199

Dear Ms. Jack:

Please refer to your March 18, 2010, Supplemental New Drug Application (sNDA), received March 22, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xenical (orlistat) 120 mg.

We acknowledge receipt of your submission dated May 18, 2010.

This "Prior Approval" supplemental new drug application provides for incorporation of the following new information into the package insert (PI) and patient package (PPI) insert regarding the occurrence of post-marketing cases of severe liver injury that have been reported rarely with the use of orlistat.

Package Insert

To the **PRECAUTIONS** section, **General** subsection, the following paragraph has been added after Table 10:

There have been rare postmarketing reports of severe liver injury with hepatocellular necrosis or acute hepatic failure in patients treated with orlistat with some of these cases resulting in liver transplant or death. Patients should be instructed to report any symptoms of hepatic dysfunction (anorexia, pruritus, jaundice, dark urine, light colored stools, or right upper quadrant pain) while taking orlistat. When these symptoms occur, orlistat and other suspect medications should be discontinued immediately and liver function tests and ALT and AST levels obtained.

To the **ADVERSE REACTIONS** section, **Other Clinical Studies or Postmarketing Surveillance** subsection, the first paragraph has been revised to read:

Other Clinical Studies or Postmarketing Surveillance

Rare cases of increase in transaminases and in alkaline phosphatase and hepatitis that may be serious have been reported. There have been reports of hepatic failure observed

with the use of XENICAL in postmarketing surveillance with some of these cases resulting in liver transplant or death. Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and symptoms have included pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption have been reported. Reports of decreased prothrombin, increased INR and unbalanced anticoagulant treatment resulting in change of hemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants. Hypothyroidism has been reported in patients treated concomitantly with orlistat and levothyroxine. Pancreatitis has been reported with the use of XENICAL in postmarketing surveillance. No causal relationship or physiopathological mechanism between pancreatitis and obesity therapy has been definitively established.

Patient Package Insert:

A new section was added:

What are the possible risks of XENICAL?

- *XENICAL has been shown to reduce the absorption of certain vitamins. You should take a multivitamin containing vitamins D, E, K, and beta-carotene once a day at least 2 hours before or after the administration of XENICAL, such as at bedtime.*
- *Some patients taking XENICAL may develop an increased risk for the development of kidney stones. Promptly report any symptoms of back pain or blood in the urine.*
- *Some patients prescribed XENICAL may already be at increased risk for the formation of gall stones. Weight loss with XENICAL can increase the risk of gall stones. Promptly report any symptoms of pain in the upper right portion of the abdomen. The pain may be accompanied by nausea and vomiting.*
- *There have been rare reports of severe liver injury in patients taking XENICAL. Promptly discontinue XENICAL and contact your healthcare provider if you develop symptoms suggestive of liver impairment, such as loss of appetite, itching, yellowing of the skin, dark urine, light colored stools, or right upper quadrant pain.*

We have completed our review of this application. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed upon labeling text.

CONTENT OF LABELING

Please resubmit the enclosed content of labeling in SPL format as soon as possible, but no later than 14 days from the date of this letter. For administrative purposes, please designate this submission, "**SPL for approved NDA 20766/S-028.**"

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
5600 Fishers Lane, Room 12B05
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81). In addition, for a period of three years, you are to submit all serious suspected cases of liver injury as expedited (15-day reports), including those describing adverse events coded with a MedDRA Preferred Term (PT) listed in the Standardized MedDRA Query (SMQ), Drug Related Hepatic Disorders – Comprehensive Search. You will also need to provide follow-up on all cases with liver injury severity scores, 3-5¹ (see reference below) to query for relevant clinical evaluation, biochemical profile, trends, and other diagnostic testing that would be necessary for analysis of causal association and risk.

If you have any questions, call Patricia Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure: Content of Labeling

¹ Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, Rochon J; DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Safety*. 2009;32(1):55-68.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
----- NDA-20766	----- SUPPL-28	----- HOFFMANN LA ROCHE INC	----- XENICAL(ORLISTAT) 120

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
05/25/2010