Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:	NDA 20-766 / S-018	**Application Type:**	sNDA
Sponsor:	Hoffmann-LaRoche, Inc	**Proprietary Name:**	Orlistat
Pharmaceutical Category:	Lipase Inhibitor	**Route of Administration:**	Oral
Indication:	Obesity management of adolescent patients aged 12 to 16 years	**Dosage:**	120mg t.i.d. with meals
Reviewer:	Theresa Kehoe, MD	**Date Review Completed:**	December 5, 2003

Chemistry Reviewer: N/A
Pharmacology Reviewer: N/A
Biopharmaceutics Reviewer: Wei Qiu, Ph.D.
Statistical Reviewer: Japo Choudhury, Ph.D.

REVIEW SUMMARY: See Executive Summary

OUTSTANDING ISSUE:

RECOMMENDED REGULATORY ACTION:

N drive location:

New clinical studies	_____	**Clinical Hold**	_____ **Study May Proceed**
NDA, Efficacy/Label supplement:	_____	**Approvable**	_____ **Not Approvable**
	X	**Approve**	

SIGNATURES: **Medical Reviewer:** Theresa Kehoe, M.D. **Date:** December 5, 2003 .

Medical Team Leader: Eric Colman, M.D. **Date:** _____ .

Clinical Review for NDA 20-766 / S-018

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Approve

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Roche should strongly consider packaging the drug product with a multivitamin for use in the adolescent population.

II. Summary of Clinical Findings

A. Current Therapeutic Options for the Treatment of Obesity in Adolescents

The are currently no approved medical therapies for obesity management in adolescents.

B. Brief Overview of Clinical Program

Orlistat, trade name Xenical, chemical name tetrahydrolipistatin, is a pancreatic lipase inhibitor that acts by inhibiting the absorption of dietary fats. Orlistat was approved for the long-term treatment of obesity on 4/23/99, for adult patients with an initial body mass index (BMI) >30 kg/m^2 or > 27 kg/m^2 in the presence of other risk factors (e. g., hypertension, diabetes, dyslipidemia).

The efficacy and safety of orlistat in pediatric patients were assessed in two studies, as outlined in the Agency's 9 August 2000 Written Request. The first was a 52-week, randomized (2:1), double-blind, placebo-controlled study of 539 obese adolescents (BMI > 97^{th} percentile). The second was a 22-day, randomized (1:1) double-blind, placebo-controlled mineral balance study in 32 obese adolescents.

C. Efficacy

In the one-year trial, approximately 65% of the patients in each treatment group completed the study. Orlistat use in the adolescent population resulted in a statistically significant decrease in BMI (-0.55 kg/m^2) when compared to placebo (+0.31 kg/m^2) (p=0.001). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had at least a 5% reduction of their baseline BMI (p=0.005), while 13.3% of orlistat-treated patients and 4.5% of placebo-treated patients had at least a 10% reduction

of their baseline BMI (p=0.002). Body weight and height increased in both groups, as one would expect in this growing population. However, the increase in body weight in the orlistat group (0.53 kg) was significantly less than the increase in the placebo group (3.1 kg) (p=0.001). Similar to results seen with BMI, significantly more patients treated with orlistat had at least 5% (19%) and 10% (9.5%) reductions in baseline body weight when compared with placebo-treated patients (11.7% and 3.3%, respectively ($p<0.05$ for both comparisons).).

In previously conducted studies of obese adults, approximately 60% of orlistat-treated patients and 31% of placebo-treated patients had at least a 5% reduction of their baseline body weight, while 27% of orlistat-treated patients and 11% of placebo-treated patients had at least a 10% reduction in body weight at one year of therapy.

Waist circumference decreased by an average of –2.6 cm in the orlistat group and by –0.6 cm in the placebo group (p=0.008). Hip circumference decreased by 1.3 cm in the orlistat-treated patients and increased by 0.1 cm in the placebo-treated subjects (p=0.01).

Fat mass and fat-free mass were directly measured by DEXA in a subgroup of 152 orlistat and 77 placebo subjects. At the end of treatment, the orlistat group had an average weight loss of –0.54 kg; whereas, the placebo subjects gained an average of 1.45 kg. Fat mass decreased by a mean of –2.4 kg in the orlistat group and increased by 0.38 kg in the placebo group (p=0.03)..

There were no statistically significant differences between treatment groups in the changes in blood pressure, lipid parameters, and glucose or insulin levels in the low risk adolescent population.

In the 3-week mineral balance investigation, 94% of the subjects in each treatment group completed the study. Positive balance was maintained for calcium, magnesium, phosphorus, and zinc in both the orlistat and placebo groups, when measured on Day 22. Copper balance was –0.4 umol/24 hr in the orlistat group and 0.1 umol/24 hr in the placebo group. Both groups had decreases in mean iron balance (-32.9 µmol/24 hour in the placebo group versus -49.7 µmol/24 hour in the orlistat group). Negative iron balance was previously noted in mineral balance studies conducted in obese adult male subjects (-10.80 ± 11.10 in the placebo treated group, -18.90 ± 10.50 in the orlistat treated group). The etiology of the net loss of iron is unclear. There was no association between gender and iron balance. No significant differences were detected between treatment groups at Day 22 for either mean serum sodium (placebo, 141.7 mmol/L; orlistat, 142.4 mmol/L) or potassium (placebo, 4.1 mmol/L; orlistat, 4.1 mmol/L). There was also no significant difference detected in mean urine sodium (placebo, 108.2 mmol/L; orlistat, 113.4 mmol/L) or potassium (placebo, 60.0 mmol/L; orlistat, 43.0 mmol/L) levels.

D. Safety

In the two adolescent studies reviewed, a total of 373 subjects received at least one dose of orlistat and 198 subjects received at least one dose of placebo. Overall, 65% of orlistat-treated patients and 63% of placebo-treated patients completed the 52-week study and 94% of both orlistat and placebo treated subjects completed the 22 day inpatient study. The calculated compliance based on pill count was 73% in the orlistat treatment group and 72% in the placebo treatment group. There were no new safety signals noted from these studies in obese adolescent subjects. Similar to studies of orlistat in obese adults, gastrointestinal adverse events including fatty/oily stools were more common in the orlistat-treated group. Fat soluble vitamin levels increased during the study in all subjects most likely because of the daily multivitamin supplementation. Vitamin levels were, however, lower in the orlistat- vs. the placebo-treated group. These differences were statistically significant for beta Carotene (3.00 μg/dl in the placebo group and 0.59 μg/dl in the orlistat group, $p = 0.001$) and Vitamin E (52.18 μmol/L in the placebo group and 11.92 μmol/Lin the orlistat group, $p = 0.089$). In the adults studies, universal multivitamin supplementation was not instituted and the use of orlistat was associated with a significant lowering of some plasma-fat soluble vitamin levels. These findings support the recommendation that all orlistat-treated patients take a daily supplement that contains all of the fat-soluble vitamins. There was no evidence that orlistat use had an impact on pulse, height, physical exam, sexual maturation, QTc interval or sex hormone levels.

E. Dosing

A single dose of orlistat, the current marketed adult dose of 120mg t.i.d., was utilized in these clinical trials in obese adolescents. The majority (88%) of subjects enrolled in these studies had a baseline body weight over 80kg, which is comparable to a normal weight adult population.

F. Special Populations

The efficacy and safety of orlistat use in the adolescent population correlates with that seen with orlistat use in the adult population. These adolescent studies enrolled subjects representing multiple races and spanned the adolescent ages from 12 – 16 years. Both male and female subjects were enrolled in these trials. Results were adequately analyzed for the effect of gender and none was found.

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/s/

David Orloff
12/10/03 04:33:50 PM
Concur with recommendation to approve this sNDA