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M E M O R A N D U M

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Re: Orlistat

Background

Xenical (orlistat), a pancreatic lipase inhibitor, was approved for the treatment of obesity in adults on April 23, 1999. On August 9, 2000, the Agency issued a Written Request for studies of orlistat in pediatric patients. Two studies were requested: 1) A 52-week randomized, double-blind, placebo-controlled study in obese adolescents aged 12 to 16 years; and 2) A 3-week, randomized, double-blind, placebo controlled mineral balance study in obese adolescents. The pediatric exclusivity board met on September 12, 2003 and it was determined that the study conducted for the supplement complied with the terms of the WR. Pediatric exclusivity was granted.

The studies were submitted to NDA 20-766 (supplement 0018) and orlistat was approved 12/12/03 for the management of obesity in adolescent patients aged 12 to 16 years.

The **INDICATION** section of labeling states the following:

“Xenical (orlistat) is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. Xenical (orlistat) is also indicated to reduce the risk for weight regain after prior weight loss. Xenical (orlistat) is indicated for obese patients with an initial body mass index (BMI) ≥ 30 kg/m² or ≥ 27 kg/m² in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).”

In addition, the **WARNINGS** section of labeling states:

“Organic causes of obesity (e.g., hypothyroidism) should be excluded before prescribing XENICAL.”

Studies performed for pediatric use:

Study 1, protocol #NM16189: Randomized, double-blind, placebo-controlled 52-week study of 539 obese adolescents, aged 12 to 16 years. All enrolled patients had a baseline body mass index (BMI) that was at least 2 units greater than the U.S. weighted mean for the 95th percentile based on age and gender. Because the patient population enrolled was anticipated to grow during the time of the study, therefore the change in BMI rather than the change in body weight was used as the primary efficacy endpoint.

Patients were maintained on a nutritionally balanced, hypocaloric diet designed to produce an initial weight loss of 0.5 to 1.0 kg/week. The caloric distribution of the diet was 30% as fat (optimally as 10% saturated, 10% monounsaturated, and 10% polyunsaturated), 50% as carbohydrate, and 20% as protein, with a maximum of 300 mg/day cholesterol and 1300 mg calcium intake per day. The maximum amount of fat in the diet was not to exceed 70 g per day. To reduce the risk for developing fat-soluble vitamin deficiencies, all participants were instructed to take a daily multivitamin at least 2 hours before or after intake of orlistat.

In a LOCF analysis, the orlistat-treated group had a decrease in the mean BMI of 0.55 kg/m² (which was in the range of weight loss that the diet alone should have caused), while the placebo-treated subjects had an increase in the mean BMI of 0.31 kg/m² (p=0.001). In a responder analysis, 27% of the orlistat-treated patients and 16% of placebo-treated subjects had a decrease of at least 5% in baseline BMI (nominal p=xx).

The orlistat group had a mean increase in body weight of 0.5 kg; whereas the placebo group had a mean increase in weight of 3.1 kg (nominal p<0.001). There was no evidence that the efficacy of the drug was significantly different in males vs. females. In a subgroup of subjects who had DEXA assessment of body composition, orlistat-induced weight loss was due primarily to a reduction in body fat. There was no evidence that fat-free mass declined following weight loss.

Three percent of patients in each treatment group reported at least one serious adverse event. Two patients from the orlistat group had serious events related to the gall bladder; one was

cholelithiasis and the other was gall bladder disorder. Both subjects had a cholecystectomy. Three percent of the subjects in the orlistat group and 2% of the placebo subjects withdrew prematurely due to an adverse event. The majority of the events leading to withdrawal in the orlistat group were gastrointestinal. Treatment-emergent adverse events were much more common in orlistat- vs. placebo-treated subjects. Fatty/oily stool, oily spotting, and oily evacuation were reported by 50% to 23% of orlistat subjects and 8% to 2% of placebo patients.

The mean serum levels of vitamins A, D, E, and beta carotene all increased from baseline to Week 52 in both treatment groups. The difference of -2.4 ug/dl in level of beta carotene between groups was statistically significant and the difference of -40.2 ug/dl in the level of vitamin E between placebo and orlistat groups was of borderline statistical significance. Fourteen percent of orlistat-treated patients and none of the placebo patients had a low vitamin A level on at least two or more consecutive measurements, and 23% of orlistat and 11% of placebo subjects had a low level of beta carotene on at least two or more consecutive measurements.

Ten placebo patients had abnormal renal ultrasounds at baseline including one patient with a renal calculus while two orlistat patients had abnormal renal ultrasounds at baseline including one patient with a renal calculus. At the end of treatment, there were no new findings in the placebo group. In the orlistat group, one patient was found to have mild left hydronephrosis and one patient had a 6 mm echogenic focus seen. A repeat renal ultrasound on that patient did not show any evidence of a renal calculus.

No patients had acute cholelithiasis during the study. Of the 343 orlistat patients who had a baseline gall bladder ultrasound, 14 had a baseline abnormality including 3 patients with gall stones and 8 patients with fatty liver infiltration or hepatomegaly. Of the 177 placebo patients who had a baseline gall bladder ultrasound, 8 had a baseline abnormality including 2 patients with gall stones, one patient was post cholecystectomy and 4 patients with fatty liver. At the end of the study, six orlistat patients were found to have asymptomatic cholelithiasis. Five of those six patients lost large amounts of weight ranging from 8.2 kg to 29.4 kg and two of those patients were sisters. A seventh patient was found to have multiple gall bladder calculi on ultrasound after complaining of flank pain at day 167 after a 15.8 kg weight loss. The patient had a subsequent cholecystectomy. One placebo patient was found to have gall stones on ultrasound at the end of the study.

Study 2, Mineral Balance Study: 3-week, randomized, double-blind, placebo-controlled, study of 32 obese adolescents. Sixteen subjects were randomized to each treatment group. Fourteen orlistat and 13 placebo subjects provided mineral balance data. The primary objective was to assess, in orlistat vs. placebo-treated subjects, the balance of the following minerals: calcium, copper, iron, magnesium, phosphorus, and zinc. Mineral balance was determined during a 24-hour period after 21 days of drug or placebo treatment. A positive 24-hour balance was noted for all minerals. Both groups had decreases in mean iron balance (-32.9 $\mu\text{mol}/24$ hour in the placebo group versus -49.7 $\mu\text{mol}/24$ 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).

Fat soluble vitamin levels increased during the study in all subjects with larger increases in the placebo-treated subjects, probably because of universal daily multivitamin supplementation. In the adult orlistat studies, universal multivitamin supplementation was not implemented and the use of orlistat in these studies was associated with a lowering of some fat soluble vitamin levels. These findings suggest that the effects of orlistat use on fat soluble vitamins can be successfully ameliorated with concomitant multivitamin usage (i.e., 2 hours before or after taking orlistat).

Obesity in Pediatrics:

Pediatric patients who are obese must be diagnosed based on BMI prior to beginning treatment. A clinically useful assessment of obesity must reflect excess body fat and still be simple to use. Body mass index (BMI), expressed as body weight in kilograms divided by the square of height in meters (kg/m²), is a weight-for-height index that meets these criteria.² BMI is the standard obesity assessment in adults, and its use in children provides a consistent measure across age groups.

Use of the 95th percentile identifies children with a significant likelihood of persistence of obesity into adulthood. In older adolescents, BMI above the 95th percentile is associated with elevated blood pressure and lipid profiles that increase the risk of obesity-related disease and mortality. Children who fit these criteria should be evaluated carefully, as described below, and treated unless some contraindication is found. A child whose BMI falls between the 85th and 95th percentile for age and sex should be evaluated carefully with particular attention to secondary complications of obesity, including hypertension and dyslipidemias. A recent large change in BMI should also prompt evaluation and possible treatment.

The first step in the assessment of an overweight child is a careful evaluation to identify any underlying syndromes or secondary complications.¹ Clinicians should identify hypertension, dyslipidemias, and tobacco use, conditions that add to the long-term cardiovascular risks conferred by obesity.² Cardiovascular disease, hypertension, or dyslipidemias in siblings, parents, aunts, uncles, and grandparents indicate increased risk for the child. Blood pressure should be measured with a cuff of an appropriate size to avoid overestimation of hypertension. Lipoprotein profile will uncover dyslipidemias. Hypertension and dyslipidemias may respond to successful weight control.

An evaluation to rule out an underlying etiology must be performed on all children presenting with obesity. Although rare, failure to diagnose these serious conditions could result in significant harm to the patient.³ Some examples of conditions that may result in

¹ Sarah E. Barlow and William H. Dietz, Obesity Evaluation and Treatment: Expert Committee Recommendations, PEDIATRICS Vol. 102 No. 3 September 1998, p. e29

² Nilsson PM, Lind L, Pollare T, Berne C, Lithell HO Increased level of hemoglobin A1c, but not impaired insulin sensitivity, found in hypertensive and normotensive smokers. *Metabolism*. 1995; 44:557-561

³ Sarah E. Barlow and William H. Dietz, Obesity Evaluation and Treatment: Expert Committee Recommendations, PEDIATRICS Vol. 102 No. 3 September 1998, p. e29

childhood obesity, and medical conditions associated with obesity are listed in the table below.

| Assessment of Medical Conditions Related to Obesity | |
|---|---|
| Findings | Potential Conditions |
| History | |
| Developmental delay | Genetic disorders |
| Poor linear growth | Hypothyroidism, Cushing's syndrome, Prader-Willi syndrome |
| Headaches | Pseudotumor cerebri |
| Nighttime breathing difficulty | Sleep apnea, obesity hypoventilation syndrome |
| Daytime somnolence | Sleep apnea, obesity hypoventilation syndrome |
| Abdominal pain | Gall bladder disease |
| Hip or knee pain | Slipped capital femoral epiphysis |
| Oligomenorrhea or amenorrhea | Polycystic ovary syndrome |
| Family history | |
| Obesity | |
| NIDDM | |
| Cardiovascular disease | |
| Hypertension | |
| Dyslipidemia | |
| Gall bladder disease | |
| Social/psychologic history | |
| Tobacco use | |
| Depression | |
| Eating disorder | |
| Physical examination | |
| Height, weight, and BMI | |
| Triceps skinfold thickness | |
| Truncal obesity | Risk of cardiovascular disease; Cushing's syndrome |
| Blood pressure | |
| Dysmorphic features | Genetic disorders, including Prader-Willi syndrome |
| Acanthosis nigricans | NIDDM, insulin resistance |
| Hirsutism | Polycystic ovary syndrome; Cushing's syndrome |
| Violaceous striae | Cushing's syndrome |
| Optic disks | Pseudotumor cerebri |
| Tonsils | Sleep apnea |
| Abdominal tenderness | Gall bladder disease |
| Undescended testicle | Prader-Willi syndrome |
| Limited hip range of motion | Slipped capital femoral epiphysis |
| Lower leg bowing | Blount's disease |

Although few studies of long-term effects of weight control in children exist, childhood obesity programs can lead to sustained weight loss when treatment focuses on behavior changes and is family-based.⁴

Obesity is a chronic disease requiring lifestyle changes including dietary and activity changes. After an initial weight-management program, the child and parent must continue to work actively for weight maintenance, weight loss, or improved BMI percentile. An effective weight-management program includes support for families during this time. Regular contact of parent and child with the clinician is essential to review and reinforce the previous goals of healthy diet and activity as well as the implementation skills. Furthermore, if obesity persists, secondary complications may emerge. Other health professionals such as school nurses, office nurses, pediatric nurse practitioners, and dietitians can help the primary clinician follow these families over time.

Discussion /Recommendations:

Orlistat is currently labeled for the treatment of obesity in patients down to 12 years of age. The current label has parameters in the indications section of labeling based on BMI. In addition, the label clearly states that organic etiologies should be ruled out before beginning Orlistat therapy.

A submission has requested the change of Orlistat from prescription to over-the-counter. This Division believes that a learned intermediary is required based on the need to:

1. Diagnose obesity
2. Rule out organic cause, and
3. Provide multidisciplinary support, including psychiatric/psychological intervention to prevent long term emotional problems and may lead to sustained weight loss.

In addition, in the adult orlistat studies, universal multivitamin supplementation was not implemented and the use of orlistat in these studies was associated with a lowering of some fat soluble vitamin levels. Because children are still growing and developing, decreased vitamins levels as well as decreased hemoglobin could have deleterious effects. While multivitamin supplementation appeared to reduce the risk for developing low fat soluble vitamin levels, a patient buying this product OTC may not also buy and use multivitamins.

OTC availability of a weight loss drug for children may be dangerous as obese pediatric patients require a multidisciplinary approach to their weight loss. There is a need for a workup to ensure that there is not an organic etiology for their weight. There are several comorbidities with obesity in kids, including hypertension, high cholesterol, and behavioral issues. Any delay in diagnosis and multidisciplinary treatment could be detrimental for the child. Any weight loss without behavioral intervention results in weight regain, and no net benefit for the child.

⁴ Epstein LH, Valoski A, Wing RR, McCurley J Ten-year follow-up of behavioral, family-based treatment for obese children. *JAMA*. 1990; 264:2519-2523

Given the current knowledge of meaningful, sustained weight management for the pediatric patient, the importance of long term management of obesity related comorbidities, and the concern of potential missed diagnosis of underlying organic etiologies, the Division of Pediatric Drug Development encourages greater consideration of factors unique to the pediatric population prior to a decision to recommend approval of an over-the counter product for use in pediatric patients.