FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

Joint Meeting of the Nonprescription Drugs and the Endocrinologic & Metabolic Drugs Advisory Committee

January 23, 2006

The National Institutes of Health's 2000 *Practical Guide: Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* defines normal weight as a body mass index (BMI) of 18.5 – 24.9 kg/m^2, overweight as a BMI of 25 – 29.9 kg/m^2, and obese as a BMI $\geq$ 30 kg/m^2.

The *Practical Guide* recommends weight loss through a combination of diet modification, increased physical activity, and behavior therapy for obese patients, and for patients who are overweight or have a high-risk waist circumference, when accompanied by two or more risk factors. In the event that lifestyle changes do not promote weight loss after 6 months, the *Practical Guide* recommends that drugs should be considered as adjunctive therapy for select patients who have a BMI $\geq$ 30 kg/m^2, or a BMI $\geq$ 27 kg/m^2 if concomitant obesity-related risk factors or disease exist.

Because overweight and obesity tend to be chronic, relapsing conditions, measures used to successfully promote clinically meaningful weight loss, including drug therapy, will need to be continued long-term if not indefinitely.

As outlined in the FDA's 1996 *Guidance for the Clinical Evaluation of Weight-Control Drugs*, and as discussed at an 8 September 2004 Endocrinologic and Metabolic Drugs Advisory Committee meeting, the Agency's approach to the approval of prescription weight-loss drugs mirrors the recommendations provided in the NIH's *Practical Guide*. For example, prescription orlistat was studied and approved for long-term weight loss in patients moderately-to-severely overweight (BMI 27 – 29.9 kg/m^2) with comorbid conditions such as hypertension, type 2 diabetes, or dyslipidemia and in obese subjects (BMI $\geq$ 30 kg/m2) regardless of the presence of comorbidities.

Limiting approval of prescription weight-loss drugs to moderately-to-severely overweight individuals with comorbidities and to obese patients maximizes the therapeutic risk – benefit profile by targeting drug therapy to individuals whose risk for weight-related disease is high and likely to outweigh the risks associated with any given pharmacological agent.

Based on the advice of the Advisory Review Panel for OTC drugs, FDA has also recognized weight control as an OTC indication and weight control products have been marketed OTC. The Advanced Notice of Proposed Rulemaking (ANPR) for Weight Control Products for Over-the-Counter Human Use based upon the Panel's recommendations was published in the *Federal Register* on February 26,1982. Two appetite suppressants, phenylpropanolamine (PPA) and benzocaine, were recommended for Category I (Generally Recognized as Safe and Effective) status in the in the ANPR. In 2000, PPA was voluntarily removed from OTC Drug products due to an increased risk of hemorrhagic stroke associated with use, and a final rule reclassifying PPA as a Category II monograph ingredient (not safe) was published A final rulemaking is in progress that will address the adequacy of available efficacy data for benzocaine for weight reduction. The ANPR for weight loss required labeling stating that the effectiveness of a weight loss product is directly related to the degree to which daily food intake is reduced and recommends nonprescription drug treatment up to 3 months to promote initial weight loss while establishing new eating habits. The monograph rulemaking allows for nine possible indications for a weight reduction product; none of these indications are based upon BMI.

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Questions

1. Has clinical effectiveness been demonstrated with orlistat 60 mg tid and 120 mg tid in the nonprescription setting? For each of these doses, please comment on the following:
    a. A 6-month duration of use
    b. Repeated use or chronic use
    c. Use in the overweight individual
    d. Use in the obese individual (with and without multiple co-morbid conditions)
    e. Use with the proposed educational materials

2. Are the safety and tolerability characteristics of orlistat 60 mg -120 mg tid acceptable for a nonprescription drug? Specifically comment on the following safety concerns and the ability of labeling to convey these concerns to the consumer.
    a. Fat-soluble vitamins
    b. Drug-drug interactions (specifically, cyclosporine and warfarin)
    c. Other concerns? (e.g., pancreatitis, liver toxicity, lithogenicity)

3. This proposed nonprescription product is targeted for overweight adults ≥ 18 yrs of age. Do you have specific concerns regarding possible use in the following populations?
    a. Pediatric patients
    b. Underweight or normal-weight individuals or in those with eating disorders
    c. Obese individuals (with and without multiple co-morbid conditions)

4. Based on data from the label comprehension study, did subjects demonstrate adequate comprehension to support safe and effective use of orlistat by consumers? Please describe the factors or data you considered in making your decision.

5. Do the results from the actual use study suggest:
    a. That consumers make correct self-selection/de-selection decisions?
    b. That consumers comply with dosing directions?

6. Do you believe that the potential benefits of nonprescription orlistat outweigh the risks?

7. Should orlistat be approved for nonprescription use?
    a. If no, please discuss the deficiencies of the clinical program.
    b. If yes, is the adult population for which orlistat is targeted in the prescription setting different from the adult population in the nonprescription setting? If so, how would each of the two populations be identified?