

## **STATEMENT ON PHENYLPROPANOLAMINE**

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### **Background**

It is accepted by the medical community and confirmed by consensus development conferences that overweight and obesity are a major medical problem because of their co-morbidities and associated risk for increased mortality. These major co-morbidities include type 2 diabetes, dyslipidemia, hypertension and atherosclerotic cardiovascular disease and stroke. Excessive weight also causes osteoarthritis, obstructive sleep apnea and alveolar hypoventilation common ailments in people with severe obesity. There are also significant psychosocial and economic consequences of being obese. Periodic National Health and Examination Surveys (NHANES) have shown a progressive increase in the prevalence of obesity in the United states over the past decade in spite of efforts at public education and the availability of foods with reduced fat content and clear nutrient composition labeling. Currently 22.5 % of the population is obese and up to 24 % of American children are overweight. Obesity afflicts in greater preponderance certain segments of the population such as African-American, Hispanic and Native-American citizens. These individuals also lag in health care access and proper nutrition counseling. Obesity also has a major impact on the cost of health care in this country. It was estimated that in 1995, the cost of treatment of obesity amounted to approximately 100 billion dollars per year. To make things worse, most people seeking treatment of obesity were not covered by their health insurance and had to pay for this treatment out of pocket.

### **Treatment of obesity**

Treatment of obesity results in major health improvement an reversal of its co-morbidities with discontinuation of treatments such as insulin therapy and anti-hypertensive drugs. This improvement may also lead to a decrease in mortality risk. Treatment of obesity involves medical or surgical approaches. The mainstay of medical treatment includes reduced calorie diets, exercise, behavior therapy, and medications that reduce appetite or decrease food absorption. Drug treatment of obesity by currently approved prescription drugs is expensive and not covered by most health insurance. PPA is the only approved over-the-counter, non-prescription appetite suppressant. Its cost is much lower than that of most prescription drugs. PPA has been recommended for short-term treatment of obesity based on studies on the efficacy and safety of the drug published periodically over the past two decades. In 11/16 double-blind placebo-controlled studies employing 900 subjects the weight loss achieved with PPA was significantly greater than placebo. Two of the most recent studies published in the early 1990's by Greenway and by our group confirmed the efficacy of the drug for short term treatment of obesity and its relative safety. Our study involved 101 subjects, 15-45 % overweight but otherwise healthy. During a double blind placebo-controlled phase, all

subjects took placebo for 2 weeks and then were randomized to placebo or PPA for 6 weeks. The subjects on PPA showed a statistically significant greater weight loss than the placebo group. A subset of these subjects chose to continue on their medication, (placebo or PPA) for a total of 20 weeks. The difference in weight loss continued; the PPA group losing 5.1 kg and the placebo group 0.4 kg by the end of the study. No difference was observed in blood pressure, pulse rate or subjective complaints between the two groups and no serious adverse events were reported.

These studies concluded that PPA is an effective and safe adjunct in the treatment of obesity. These studies, because of their design, were considered by the FDA to be the most convincing evidence of the effectiveness and safety of PPA in the treatment of people with mild or moderate obesity. The degree of weight loss achieved with PPA was comparable to that obtained with currently approved prescription drugs.

### **Comment on the studies on PPA and risk of hemorrhagic stroke**

I have reviewed the final report of the "Hemorrhagic stroke project" by Horowitz et al. This was a study to investigate the possibility that the use of PPA for weight reduction was associated with a higher incidence of hemorrhagic stroke. What this study shows is that hemorrhagic stroke is quite rare among PPA users. It is likely from these data that subjects that took PPA had risk factors for hemorrhagic stroke, not shared by the control group. Among the patients who took PPA and sustained hemorrhagic stroke only one met the definition of obesity with a BMI of 31. One other subject was in the overweight category, BMI 27.49 but the rest were either of normal weight or underweight, suggesting the possibility that PPA was used inappropriately by these subjects. It is important to consider the fact that other commonly available over-the-counter drugs such as aspirin could cause serious complications if taken inappropriately. For example, it could cause upper gastrointestinal bleeding in somebody with peptic ulcer disease or gastritis. In addition, any assessment of potential risks must take into account the significant benefit conferred by PPA when used as an appetite suppressant.

### **Conclusion**

Obesity is a serious chronic medical disease without effective cure. Weight reduction improves morbidity and mortality. As with other pharmacological treatments, idiosyncratic reactions may lead to serious side effects. These side effects depend on pharmacogenetic variability and frequency of risk factors among patients. The low incidence of side effects with PPA relative to the benefits of weight reduction should help place this issue into proper perspective.

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