M E M O R A N D U M DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

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FROM: Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food & Drug Administration

TO: Members and Consultants,
Endocrinologic & Metabolic Drugs Advisory Committee

SUBJECT: 13 June 2007, Advisory Committee meeting for rimonabant (Zimulti™)

Thank you for agreeing to participate in the June 13, 2007, advisory committee meeting for rimonabant, a first-in-class cannabinoid receptor 1 (CB1) antagonist/inverse agonist, being developed by Sanofi-Aventis for weight management.

Based on the review of data submitted in the rimonabant new drug application (NDA) in 2005, we concluded that the drug was effective for weight management, as defined by our obesity drug guidance document, but did not believe that sufficient evidence had been provided to adequately assess the compound's potential risks. In particular, we were concerned about associations between rimonabant and increased rates of psychiatric adverse events, including depression and suicidality, and neurological adverse events, including seizures. These concerns and the action/information needed to address them were detailed in the Division's February, 2006, approvable letter to Sanofi-Aventis.

The company submitted their response to the approvable letter in October, 2006. Following review of the NDA resubmission, we remained concerned about rimonabant's adverse event profile, specifically adverse psychiatric reactions, and therefore decided to convene an advisory committee to publicly discuss and seek recommendations concerning the potential benefits and harms of rimonabant.

The assessment of rimonabant's weight-loss efficacy comes principally from four placebo-controlled trials: RIO North America, RIO Europe, RIO Diabetes, and RIO Lipids. In these trials, rimonabant 20 mg once-daily along with a mildly hypocaloric diet, was shown to reduce body weight by approximately 5% relative to diet alone during one-year trials of more than 6000 moderately overweight and obese subjects. As with other obesity drugs, the weight-loss efficacy of rimonabant was attenuated in subjects with type 2 diabetes. Rimonabant-associated weight loss tended to be accompanied by improvements in levels of triglycerides (TG), high density lipoprotein cholesterol (HDL-C), fasting insulin, and HbA1c in subjects with type 2 diabetes. The drug had no effect on

levels of total cholesterol or low density lipoprotein cholesterol (LDL-C), and for unclear reasons, reductions in systolic and diastolic blood pressure were less than expected given the degree of weight loss.

The safety database for rimonabant is large and growing. As of 18 December 2006, approximately 13,000 subjects have been exposed to at least one dose of rimonabant in completed studies (many from smoking cessations trials). Thousands more are enrolled in ongoing trials. The CRESCENDO study alone has randomized more than 8000 of a planned 17,000 individuals with abdominal obesity to rimonabant 20 mg or placebo to examine, over the course of 5 years, whether the drug's favorable effects on body weight, HDL-C, TG, and HbA1c translate into lower risk for myocardial infarction, stroke, or cardiovascular death. The study is scheduled for completion in early 2010.

As mentioned above, thus far, psychiatric adverse events represent the most common and worrisome rimonabant-induced adverse events. According to data generated by the company, the incidence of depressed mood disorders was roughly doubled in subjects who received rimonabant 20 mg in the RIO trials. This imbalance in depressive disorders led us, in conjunction with members of the Agency's Office of Biostatistics and Dr. Kelly Posner of Columbia University, to conduct retrospective meta-analyses of suicidality, similar to what was done by us to examine the relationship between suicidality and antidepressants in adolescents and adults with major depressive disorders. The overall odds ratio for suicidality for rimonabant was 2.0 (95% CI: 1.2, 3.4). We anticipate that much of the discussion at the advisory committee meeting will center on the relationship between rimonabant and depression, and on the methodology, results, and interpretation of FDA's meta-analytic assessment of suicidality from completed rimonabant studies.

Other safety issues that we plan to discuss include the increased incidence of anxiety-related disorders in subjects treated with rimonabant, the neurological adverse event profile of patients treated with the drug, and the apparent discordance between preclinical data in which rimonabant is strongly proconvulsant and clinical data which to date do not provide a clear signal for seizure risk.

As you read the meeting background material from Sanofi-Aventis and FDA, we ask that you keep the following draft questions in mind.

1a. Do you believe that rimonabant causally increases the incidence of:

- Suicidality?
- Psychiatric adverse events other than suicidality?
- Neurological adverse events other than seizures?
- Seizures?

1b. If yes to the above, do you believe that the increases are, or will be, clinically important?

2a. Do you believe that the currently available data sufficiently characterize rimonabant's safety profile?

2b. If no, please discuss what additional data should be obtained.

3a. Based on the currently available data, do you believe rimonabant has a favorable risk-benefit profile and should be approved for the indication of weight management in individuals with a body mass index of $\geq$ 30 kg/m^2 and $\geq$ 27 kg/m^2 when accompanied by at least one comorbid condition?

3b. If no, please explain why and discuss what additional information the sponsor could obtain that might improve rimonabant's risk-benefit profile.

3c. If yes, are there specific labeling recommendations that you have?

Once again we thank you for your participation in the FDA's advisory committee process. We are looking forward to an interesting meeting on June 13th.