INTRODUCTION
The prevalence of obesity continues to rise. Current data indicate that the combined prevalence of overweight and obesity in adults in the U.S. is 66.3%. The prevalence for obesity alone in adults is 32.2%; for extreme obesity in adults, this figure is 4.8%. Approximately 17.1% of children and adolescents in the U.S. are overweight.

Overweight is defined as a body mass index (BMI) of 25 to 29.9 kg/m²; obesity is defined as a BMI of 30 kg/m² or greater. Obesity is a significant risk factor for the development of insulin resistance, type-2 diabetes mellitus, hypertension, hyperlipidemia, cardiovascular disease, and stroke. Furthermore, it is a contributing factor for pulmonary hypertension, sleep apnea, nonalcoholic fatty liver disease, gallbladder disease, hyperuricemia and gout, osteoarthritis, and certain types of cancer.

The exact causes of obesity are unknown, but obesity is believed to be a complex interaction between genetic, environmental, and psychosocial factors. The goal of antiobesity treatment includes not only a reduction in weight but also in the disability and morbidity associated with obesity, thus leading to an improved quality of life for patients. Healthy lifestyle changes, including a reduced caloric intake and increased physical activity, are the mainstays of treatment. Because obesity is continuing to become more prevalent, there is a growing interest in finding alternative treatments, including pharmacological therapies.

Clinical practice guidelines from the American College of Physicians consist of five recommendations for the treatment of obesity:

- All obese patients should be counseled on lifestyle and behavioral modifications.
- Pharmacological therapy should be offered to patients who have failed to achieve weight loss through diet and exercise alone. Health care providers should discuss the side effects, lack of long-term safety data, and the temporary nature of the weight loss achieved before medication is prescribed.
- Adjunctive drug therapy options include sibutramine (Meridia, Abbott), orlistat (Xenical, Sanofi-Aventis), phentermine (Adipex, Gate), diethylpropion (Tenuate, Sanofi-Aventis), fluoxetine (Prozac, Eli Lilly), and bupropion (GlaxoSmithKline).
- Patients with a BMI of 40 kg/m² or above who have failed to improve with diet and exercise, with or without adjunctive medications, and who have obesity-related comorbid conditions should be considered for surgery.
- Patients should be referred to high-volume medical centers with surgeons experienced in bariatric surgery.

Rimonabant (Acomplia, Sanofi-Aventis) is a new investigational drug in a new class of therapeutic agents called cannabinoid-1 (CB1) receptor blockers. In February 2006, the Food and Drug Administration (FDA) issued an approvable letter for weight management. Final approval for weight loss is pending because of an undisclosed requirement by the FDA. The company has not chosen to reveal the content of the letter for this indication. However, rimonabant did receive marketing authorization by the European Commission on June 21, 2006. In Europe, this drug is indicated as an adjunct to diet and exercise for the treatment of obese or overweight patients with associated risk factors, such as type-2 diabetes or dyslipidemia.

CHEMICAL AND PHYSICAL PROPERTIES/MECHANISM OF ACTION

Rimonabant [N-piperino-5-(4-chlorophenyl)-1-1(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide] is a CB1 antagonist. At low concentrations, it may also act as an inverse agonist. At very high concentrations, rimonabant also behaves as a CB2 receptor antagonist, blocks calcium and potassium channels, and may directly affect cellular gap junctions.

Cannabinoid receptors are members of the G-protein coupled receptor (GPCR) superfamily of cell–surface heptahelical receptors. There are currently two types of cannabinoid receptors: CB1 and CB2. CB1 receptors are among the most abundant GPCRs in the brain.

The cannabinoid CB1 receptors are members of the Gi/Go-linked GPCR family. Therefore, activation of these receptors by anandamide (an endogenous cannabinoid agonist) results in suppression of neuronal excitability and in a release of neurotransmitters. This effect appears to be accomplished through the
following mechanisms: inhibition of adenylyl cyclase, inhibition of voltage-sensitive calcium channels, activation of inwardly rectifying potassium channels, and activation of MAP kinase.\textsuperscript{14}

Because of the strong presynaptic localization of the CB\(_1\) receptors and their inhibition of the calcium channels and adenylyl cyclase, it is thought that the primary function of these receptors is to inhibit neurotransmitter release, specifically gamma-aminobutyric acid (GABA) or glutamate.\textsuperscript{14} In a process called retrograde signaling, endocannabinoids are thought to regulate the release of GABA and glutamate. It is theorized that the endocannabinoid system may be overactive in some individuals with obesity, thus contributing to the accumulation of weight and also encouraging nicotine discrimination (preferring it to other compounds).\textsuperscript{15}

Stimulation of the CB\(_1\) receptors is thought to affect central and peripheral action on lipid and glucose metabolism in adipose tissue. Rimonabant helps to regulate food intake, modulates the intake of highly palatable sweet or fatty foods, affects energy balance, and influences nicotine dependence.\textsuperscript{16,17}

**PHARMACOKINETICS\textsuperscript{18,19}**

Little pharmacokinetic information on rimonabant has been published. Only one poster from a meeting in 2006 described the drug’s pharmacokinetic properties.\textsuperscript{18} It is reported that dose proportionality does not appear to deviate with this agent when it is given in doses up to 20 mg/day. After that point, there is a less than dose-proportional increase in exposure.

The bioavailability of rimonabant is unknown. The time to maximum concentration (\(T_{\text{max}}\)) is approximately two hours, and the peak concentration (\(C_{\text{max}}\)) is 196 ± 28.1 ng/ml. The volume of distribution (\(V_d\)) is larger and the time to steady state is longer in obese individuals (25 days) than in non-obese individuals (13 days). The \(C_{\text{max}}\) and the area-under-the-curve (AUC) concentration are increased when the drug is taken with a high-fat meal. The plasma protein binding of rimonabant in vitro is high, at more than 99%.

Rimonabant is metabolized by the cytochrome (CYP) 3A enzyme and amidohydrolase pathways in vitro. Administration of ketoconazole (Nizoral, Janssen) with rimonabant resulted in an increase in the AUC by 104% (40%–197%).\textsuperscript{19}

When combined with CYP 3A4 inhibitors, plasma levels of the drug would be expected to increase; therefore, caution with the use of known CYP 3A4 inhibitors is warranted. Although CYP 3A4 inducers have not been investigated, it is anticipated that they would reduce the drug’s plasma levels and, possibly, its efficacy. Rimonabant does not induce or inhibit common CYP enzymes or P-glycoprotein in vitro.\textsuperscript{19} It is a mild inhibitor of CYP 2C8. Metabolites of rimonabant do not contribute to the medication’s effects. Most of the drug (about 86%) is eliminated in the feces unchanged and as metabolites.

The drug’s half-life is longer in obese patients (approximately 16 days) than in non-obese patients (nine days); this difference is believed to result from the larger \(V_d\) of obese people. A patient’s sex has no effect on rimonabant’s pharmacokinetics.

Table 1 summarizes the pharmacokinetic parameters of rimonabant.

**EFFICACY IN CLINICAL TRIALS**

Four published clinical trials have assessed the efficacy and safety of rimonabant in the treatment of obesity and cardiometabolic risk factors.\textsuperscript{20–23} Other studies of the drug have been presented as posters at clinical meetings, but they are not reviewed in this article.

The Rimonabant In Obesity (RIO) Program consists of four published clinical trials\textsuperscript{20–23} comparing rimonabant 5 mg and 20 mg with placebo. RIO–Lipids and RIO–Diabetes were one-year trials; RIO–Europe and RIO–North America were two-year trials. Results of RIO–Lipids, RIO–Diabetes, and RIO–North America, as well as the first-year results of RIO–Europe, have been published.

**Després et al. and the RIO–Lipids Study\textsuperscript{20}**

Després et al. conducted a randomized, double-blind study for 12 months to evaluate the efficacy and safety of rimonabant in overweight or obese patients (BMI, 27–40 kg/m\(^2\)) with untreated dyslipidemia. Patients included in the study, called Rimonabant in Obesity–Lipids (RIO–Lipids), were required to have fasting plasma triglyceride levels of 1.7 to 1.79 mmol/L (150 to 700 mg/dl), a ratio of total cholesterol to high-density lipoprotein-cholesterol (HDL-C) above 5 for men and above 4.5 for women, or both.

Patients were excluded for the following reasons:

- if they had a history of pharmacological treatment for dyslipidemia within the previous six weeks
- if they had taken medications for weight loss within the past three months
- if they had followed a very-low-calorie diet during the previous six months before screening
- if they had diabetes mellitus or severe depression

A total of 1,036 patients were randomly assigned to the following groups: placebo (\(n = 342\)), rimonabant 5 mg (\(n = 345\)) once daily, or rimonabant 20 mg (\(n = 346\)) once daily. In the intention-to-treat-pop-
ulation (ITT)/last-observation-carried-forward (LOCF) analyses, patients receiving rimonabant 20 mg lost 6.9 kg; with rimonabant 5 mg, they lost 3.1 kg; and with placebo, they lost 1.5 kg.

The net weight loss for patients receiving rimonabant 20 mg, when adjusted for placebo, was 5.4 kg. A significant decrease in weight loss was observed in the two rimonabant treatment groups, compared with the placebo group, at the end of the 12 months. The proportion of patients who lost 10% or more of their weight was 32.6% with rimonabant 20 mg; the proportion of those who lost the same amount of weight was 7.2% with placebo (P < 0.001).

Weight loss occurred during the first nine months of the study period, and a plateau was observed for the remaining three months without weight being regained. In waist circumference, a significant decrease of 7.1 cm was observed with rimonabant 20 mg; a reduction of 3.5 cm was seen with 5 mg; and a decrease of 2.4 cm occurred with placebo (P = 0.029).

A significant increase in HDL-C levels was noted for both rimonabant doses (19% with 20 mg, 14% with 5 mg), compared with 11% for placebo (P = 0.025). Triglyceride levels remained stable with rimonabant 5 mg and placebo but decreased by 12% when the dose was 20 mg.

Although the result was not significant, LDL-C levels increased by approximately 7% in all three study groups.

Reductions in fasting glucose were not observed in any of the groups. The prevalence of the metabolic syndrome was significantly reduced by 41% in the patients receiving rimonabant 20 mg because of the reduction in waist circumference and the increase in HDL-C levels.

Adverse drug events (ADEs), reported in 5% or more of the rimonabant-treated patients, included nausea, dizziness, influenza, anxiety, diarrhea, and insomnia, and they occurred early in the study period. These ADEs were more common in patients receiving rimonabant 20 mg. More patients in the 20-mg group discontinued the study because of ADEs, compared with patients in the other two groups.

The most frequently occurring ADEs leading to discontinuation from the study were nausea (1.2% of patients receiving 20 mg, in 0.6% with 5 mg, and in 0% with placebo) and psychiatric disorders, including depression (in 2.9% of patients receiving 20 mg, in 1.7% given 5 mg, and in 0.6% given placebo) and anxiety (in 1.7% of patients receiving 20 mg, in 0.3% with 5 mg, and in 0.6% with placebo).

Van Gaal et al. and the RIO–Europe Study

A two-year, multicenter, randomized, double-blind, placebo-controlled study (RIO–Europe) was conducted to assess the efficacy and safety of rimonabant 5 and 20 mg in reducing body weight and improving cardiovascular risk factors in overweight or obese individuals. Obese patients over the age of 18 with a BMI of 30 kg/m² or more and overweight patients with a BMI of 27 kg/m² or more with treated or untreated hypertension or with treated or untreated dyslipidemia participated in the study. Patients were excluded from the study if they had diabetes mellitus; cardiovascular, pulmonary, hepatic, or renal disorders; and substantial neurological and psychological illness.

The primary endpoint of the study was the change in weight from baseline in the ITT/LOCF population after one year of treatment. A total of 1,507 patients received placebo (n = 305), rimonabant 5 mg (n = 603), or rimonabant 20 mg (n = 599) once daily with a hypocaloric diet of 600 kilocalories/day. Patients underwent a two-week screening period, followed by a four-week single-blind, placebo-run-in period.

Nine hundred twenty patients (66%) completed the one-year follow-up phase: placebo, 178 patients (58.4%); rimonabant 5 mg, 379 patients (62.7%); and rimonabant 20 mg, 363 patients (60.6%).

In the ITT/LOCF population, a significantly greater mean weight loss from baseline was observed with rimonabant 5 mg (~3.4 kg, P = 0.002) and 20 mg (~6.6 kg, P < 0.001) than with placebo (~1.8 kg).

A significant decrease in waist circumference from baseline was also observed with 5 mg (~3.9 cm, P = 0.002) and 20 mg (~6.9 cm, P < 0.001), compared with placebo (~2.4 cm).

Significantly more patients in the two rimonabant groups who completed the study also achieved a weight loss of 5% or more from baseline, compared with the placebo group (67.4% with rimonabant 20 mg; 44.2% with rimonabant 5 mg; and 30.5% with placebo). However, the proportion of patients achieving a weight loss of 10% or more from baseline was greater with 20 mg (39%) than with placebo (12.4%, P < 0.001), but no difference was found between rimonabant 5 mg (15.3%) and placebo (12.4%).

Compared with patients receiving placebo, the 20-mg group showed significant improvements in levels of HDLC, triglycerides, fasting plasma glucose, and insulin.

Most ADEs were reported with the 20-mg dose of rimonabant. Nausea was reported by 13% of patients receiving 20 mg, by 5% receiving 5 mg, and by 4% receiving placebo. The percentages of patients discontinuing the study because of ADEs were 14.5% (87 patients) receiving 20 mg, 8.3% (50 patients) receiving 5 mg, and 9.2% (28 patients) receiving placebo.

Of the 87 patients who discontinued rimonabant 20 mg during the trial, approximately 50% (42 patients, or 7% of all patients receiving that dose) did so because of psychiatric disorders, with depression being the most common (22 patients, or 3.7%).

Pi-Sunyer et al. and the RIO–North America Study

In the two-year, randomized, double-blind, placebo-controlled RIO–North America trial, Pi-Sunyer et al. compared the safety and efficacy of rimonabant with placebo in obese adults with a BMI of 30 kg/m² or more and in overweight adults with a BMI of 27 kg/m² or more with treated or untreated hypertension or dyslipidemia. Patients with diabetes mellitus were excluded from this study.

At the end of one year, the investigators performed efficacy analyses using the ITT/LOCF population to determine weight loss and, at the end of two years, whether patients had avoided regaining weight. After a four-week run-in period, with a total of 3,045 patients, 607 received placebo, 1,216 received rimonabant 5 mg, and 1,222 received rimonabant 20 mg once daily in conjunction with a low-calorie diet and exercise.

After one year, 51% of the placebo and rimonabant 5-mg patients completed the study. The 20-mg group had a slightly higher completion rate of 55%.
Patients lost significantly more weight with rimonabant 5 mg and 20 mg than with placebo. The percentage of patients achieving a weight loss of 10% or more was 25.2% with rimonabant 20 mg and 8.5% with placebo ($P < 0.001$). Only 10.6% of the 5-mg patients lost 10% or more of their baseline body weight.

The rimonabant 20-mg group experienced a greater decrease in waist circumference (~6.1 cm vs. ~2.5 cm with placebo; $P < 0.001$); a greater decrease in triglyceride levels (~5.3% vs. 7.9% with placebo; $P < 0.001$); and a greater increase in HDL-C levels (12.6% vs. 5.4% with placebo; $P < 0.001$).

At the end of one year, patients receiving rimonabant 20 mg were randomly reassigned to continue taking the 20-mg dose or to receive placebo for a one-year follow-up period; patients taking placebo continued with the same treatment.

In the two-year ITT-LOCF population, the patients who remained on rimonabant 20 mg maintained a mean weight loss of 7.4 kg from their baseline weight; the patients who were reassigned to receive placebo regained most of their weight previously lost. Seventeen percent of patients receiving rimonabant 20 mg achieved a weight loss of 10% or more, compared with 8% of placebo patients.

After two years, the mean decrease from baseline in waist circumference was also greater in those receiving rimonabant 20 mg (~5.0 cm) than in the placebo group (~2.2 cm) ($P < 0.001$).

In terms of cardiometabolic risk factors in the second year of the study, patients receiving placebo had decreased levels of HDL-C and increased levels of triglycerides. A continued increase in the level of HDL-C from baseline was observed in those who received placebo or rimonabant 20 mg for two years, but the increase was significantly greater for patients taking rimonabant ($P < 0.001$). Triglyceride levels and features of the metabolic syndrome declined more from baseline with rimonabant 20 mg than with placebo ($P < 0.001$).

The percentage of patients who withdrew from the study after the first year because of ADEs was greater in those taking rimonabant 20 mg (12.8%), compared with those taking rimonabant 5 mg (9.4%) and placebo (7.2%). ADEs leading to discontinuation from the study in all treatment groups consisted of psychiatric, nervous system, and gastrointestinal tract effects. It was interesting that 6.2% of the rimonabant 20-mg patients discontinued the study because of psychiatric disorders, compared with 2.3% of the placebo patients. The overall rates of ADEs, withdrawal rates, and ADEs leading to withdrawals from the study were lower in the second year than in the first year.

The trial authors concluded that the significant weight loss achieved with rimonabant at the end of one year was well maintained during the second year in patients receiving rimonabant treatment over two years, and a favorable effect on cardiometabolic risk factors was seen.

**Scheen et al. and the RIO–Diabetes Study**

A multicenter, randomized, double-blind, placebo-controlled study of one year’s duration evaluated the efficacy and safety of rimonabant in combination with diet and exercise in overweight or obese patients with type-2 diabetes who had been treated with metformin or sulfonylurea monotherapy for at least six months. To be eligible for the study, patients had to have a glycosylated hemoglobin (HbA1c) between 6.5% and 10% and a fasting glucose concentration between 100 and 271 mg/dl (5.5 and 15.04 mmol/l). A total of 1,045 patients were assigned to receive rimonabant 5 mg once daily (358), rimonabant 20 mg once daily (339), or placebo (348). After one year of treatment, ITT data showed that the weight change from baseline was significantly greater in patients receiving rimonabant 5 mg (~2.3 kg, $P = 0.001$ vs. placebo) and rimonabant 20 mg (~5.3 kg, $P = 0.001$ vs. placebo) compared with placebo (~1.4 kg). A net weight loss of 3.9 kg was achieved with the 20-mg dose.

A significant reduction in waist circumference was also observed with both rimonabant doses compared with placebo. The mean HbA1c change from baseline was ~0.6% for the rimonabant 20-mg group, whereas patients receiving placebo experienced an increase of 0.1% ($P < 0.0001$). More of the rimonabant 20-mg patients achieved a HbA1c level of below 7%, compared with patients receiving placebo ($P < 0.0001$). Significantly greater improvements in fasting glucose, HDL, triglycerides, and non-HDL levels were observed with rimonabant 20 mg than with placebo ($P < 0.0001$ for all).

As with the other studies, the most common ADEs occurring in 5% or more of patients were nausea, diarrhea, vomiting, dizziness, hypoglycemia, fatigue, and anxiety. These ADEs were mild to moderate and generally occurred during the early stages of treatment. Depressed mood disorders, nausea, and dizziness were the most common ADEs leading to discontinuation of treatment in patients receiving rimonabant 20 mg.

The authors concluded that the RIO–Diabetes trial demonstrated that rimonabant at a dose of 20 mg/day, in combination with diet and exercise, could significantly reduce body weight and waist circumference and improve HbA1c levels as well as various cardiovascular and metabolic risk factors in overweight or obese patients with type-2 diabetes that has not been adequately controlled with metformin or sulfonylurea monotherapy.

**SERENADE**

The Study Evaluating Rimonabant Efficacy in Drug-Naïve Diabetic Patients (SERENADE) compared the effectiveness of rimonabant 20 mg once daily with placebo in improving blood glucose control, indicated by HbA1c. This study was presented at the International Diabetes Federation World Diabetes Congress in Cape Town, South Africa, in December 2006. Patients were enrolled in the study according to the following criteria:

- if they had a diagnosis of type-2 diabetes for at least two months but less than three years
- if their HbA1c levels were between 7% and 10%
- if they had not previously used antidiabetic medications within six months before rimonabant therapy

Patients receiving rimonabant 20 mg once daily demonstrated a significant decrease in HbA1c levels (0.8%), from a baseline of 7.9%, compared with a 0.3% decrease in patients receiving placebo ($P = 0.002$). In patients with baseline HbA1c levels of 8.5% or above, a significantly greater reduction in HbA1c levels was observed with rimonabant 20 mg (1.9%) than with placebo (0.7%).

Patients in the rimonabant 20-mg group lost 6.7 kg; those in the placebo...
The most common ADEs were diziness (10.9% with rimonabant 20 mg vs. 2.1% with placebo), nausea (8.7% with 20 mg vs. 3.6% with placebo), upper respiratory tract infection (7.2% with 20 mg vs. 2.7% with placebo), anxiety (5.8% with 20 mg vs. 3.6% with placebo), and depressed mood (5.8% with 2 mg vs. 0.7% with placebo).

The most common ADEs leading to withdrawal from the study were nausea (2.2% with rimonabant 20 mg vs. 0% with placebo), depressed mood disorder (2.2% with 20 mg vs. 0% with placebo), and paraesthesia (2.2% with 20 mg vs. 0% with placebo).

CONCLUSION

Rimonabant offers a unique therapeutic approach for appetite control and weight reduction. It has demonstrated efficacy in sustaining weight loss but has also been associated with higher rates of psychiatric side effects, such as anxiety and depression, compared with placebo. These psychiatric side effects may significantly limit rimonabant’s use in certain patients.

Sanofi-Aventis filed for regulatory approval with the FDA in April 2005, hoping to have rimonabant ready for a 2006 launch. However, in February 2006, the FDA declined to issue a final approval and is still waiting until a number of unspecified issues are resolved. The FDA did grant rimonabant a “non-approvable” letter for its use as an aid for smoking cessation. As of this writing, the date of a final approval for rimonabant remains unclear, but it may be sometime in 2007.

REFERENCES


