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Rimonabant

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Contents

Abstract

▲ Rimonabant is the first of a new class of selective cannabinoid receptor-1 blockers. It reduces the overactivity of the endocannabinoid system, improving lipid and glucose metabolism and regulating food intake and energy balance.

▲ In four randomised, double-blind clinical trials in overweight or obese adults with or without type 2 diabetes and/or dyslipidaemia, oral rimonabant 20mg once daily reduced weight and waist circumference to a significantly greater extent than placebo.

▲ A significantly greater proportion of rimonabant than placebo recipients achieved the clinically significant weight-loss target of ≥5% or ≥10% of initial weight.

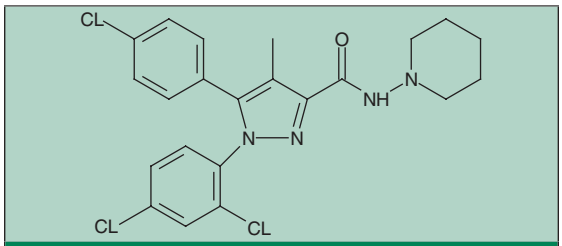
▲ Rimonabant was associated with significant improvements in glycaemic control relative to placebo, with ≈57% of the reduction in glycosylated haemoglobin being independent of the effects of weight loss in one trial.

▲ Improvements in other cardiometabolic risk factors (i.e. increases in high-density lipoprotein-cholesterol [HDL-C] and decreases in triglyceride [TG] levels) were significantly greater with rimonabant than with placebo.

▲ The improvement in lipid profile also demonstrated a weight-independent effect, with ≈47–58% of the improvement in HDL-C and TG being beyond that expected through weight loss alone.

▲ Rimonabant was generally well tolerated, with most adverse events considered mild to moderate in severity.

Features and properties of rimonabant (Acomplia®)	
Indication	
As an adjunct to diet and exercise in the treatment of obese patients (body mass index [BMI] ≥30 kg/m^2), or overweight patients (BMI >27 kg/m^2) with associated risk factor(s) such as type 2 diabetes or dyslipidaemia	
Mechanism of action	
Selective cannabinoid receptor-1 blocker	
Dosage and administration	
Dose	20mg
Frequency of administration	Once daily before breakfast
Route of administration	Oral
Pharmacokinetic parameters after administration of rimonabant 20mg once daily for 21 days (lean volunteers; obese patients)	
Maximum plasma concentration (C_{max})	196 ng/mL (steady-state); 188 ng/mL
Time to C_{max}	≈2h; ≈2h
Area under the drug concentration-time curve	2960 ng • h/mL (steady-state); 2480 ng • h/mL
Elimination half-life	≈9 days; ≈16 days
Most common treatment-related adverse events (≥10% of patients in pooled clinical trials)	
Nausea, upper respiratory tract infection	



Rimonabant

Chronic diseases for which overweight and obesity are major risk factors include type 2 diabetes mellitus, hypertension, stroke, dyslipidaemia, osteoarthritis, cardiovascular disease, sleep apnoea, respiratory problems and some cancers,[1] establishing obesity as a major contributor to the chronic disease and disability burden worldwide.

Concomitant with weight loss in obese and overweight individuals is a decrease in the risk factors for type 2 diabetes and cardiovascular disease; reductions in blood pressure (BP), improvements in plasma lipid profile and reductions in plasma glucose and glycosylated haemoglobin (HbA_{1c}) levels are seen in many obese and overweight patients who achieve weight loss.[2] A weight loss of 5–10% of initial bodyweight is considered sufficient in order to confer a clinically significant improvement in these factors in obese patients.[3] Pharmacotherapy as an adjunct to diet and exercise is recommended in patients with a body mass index (BMI) ≥30 kg/m^2 with no additional risk factors or diseases, or in patients with a BMI ≥27 kg/m^2 with additional risk factors and/or diseases.[2]

The endocannabinoid system is composed of an endogenous group of short-lived, phospholipid-derived agonists, including anandamide and 2-arachidonoylglycerol (2-AG), and two types of cannabinoid (CB) receptors (CB-1 and CB-2).[4-6] In humans and animals, CB-1 is expressed in the brain and adipose tissue;[7,8] in animals, CB-1 is also found in peripheral tissues such as the gastrointestinal tract,[6,7] liver,[9] muscle[10] and pancreas.[11] CB-2 is predominantly expressed on immune cells.[7]

Stimulation of the receptors of the endocannabinoid system regulates energy balance via alteration of the metabolism of glucose and lipids in adipose tissue, both centrally and peripherally,[5,6,12] and promotes increased food intake and weight gain.[7] The endocannabinoid system is overactivated in animal models of obesity and in obese patients; higher tissue levels of anandamide and 2-AG are found in the liver[9] and pancreas[11] of obese mice, while higher levels of 2-AG are found in visceral fat in obese patients compared with patients of healthy weight.[11,13] In addition, higher circulating levels of both anandamide and 2-AG are found in obese patients with type 2 diabetes compared with healthy individuals.[11]

Rimonabant (Acomplia®)[1] is the first of a new class of selective endocannabinoid receptor blockers, acting to selectively inhibit the action of central and peripheral CB-1 receptors, thereby improving lipid and glucose metabolism and regulating food intake and energy balance.[5] This profile examines the pharmacological properties and tolerability of rimonabant and reviews its clinical efficacy in the treatment of obese or overweight patients with or without concomitant obesity-related comorbidities such as type 2 diabetes or dyslipidaemia. Some data contained in this review were obtained from the manufacturer, and are cited as data on file.[14]

1. Pharmacodynamic Profile

Most data on the pharmacodynamics of rimonabant discussed in this section were obtained from *in vitro* and *in vivo* model systems;[8,10,15-27] only limited data are available from trials in humans.[28] The effect of rimonabant on plasma lipid and insulin levels in obese patients are discussed in section 3.

- *In vitro*, rimonabant is a CB receptor blocker with 1000-fold higher affinity for the CB-1 receptor than the CB-2 receptor;[16] it inhibits the proliferation and maturation of adipocytes.[20]
- Rimonabant has demonstrated a long duration of action in mice, with 50% of brain CB-1 remaining

1 The use of trade names is for product identification purposes only and does not imply endorsement.

occupied 8 hours after oral administration of rimonabant 10 mg/kg.[15]

- Rimonabant reduces food intake, adiposity and bodyweight in obese mice.[26] It modulates several peripheral signals in rodents (ghrelin,[18] leptin[19,22] and adiponectin [a potentially important, adipose tissue-derived cytokine with antidiabetic and antiatherosclerotic properties][8,19]) that modulate food intake and energy expenditure. In mice, rimonabant attenuates the 2-AG mediated increase in food intake.[22,23]
- Rimonabant also alters the metabolic activity of adipose tissue *in vivo* in rodents.[8,10,17] CB-1 receptor expression is upregulated in the adipose tissue of obese rats compared with lean rats.[8] Rimonabant significantly ($p < 0.01$) increased expression of adiponectin in the adipose tissue of these rats compared with vehicle-treated animals, but had no effect in lean rats.[8] The increase in adiponectin was mediated by CB-1, with the induction of expression lost in CB-1 receptor knockout mice.[8]
- In a phase III clinical trial[28] (see section 3), plasma adiponectin levels increased (46%; $p < 0.001$ vs placebo) after 1 year of treatment with rimonabant 20 mg/day, an effect that was partially independent of weight loss;[28] leptin levels decreased (23%; $p < 0.001$ vs placebo) after the same treatment period.[28]
- Rimonabant also reduces plasma insulin levels,[19] serum levels of glucose, triglycerides (TGs) and low-density lipoprotein-cholesterol,[19] and inhibits lipoprotein lipase[21] in rodent models.
- Rimonabant treatment significantly increased glucose uptake in the skeletal muscle of obese mice compared with that in vehicle-treated animals (13.1 vs 7.8 μmol/h/g; $p < 0.05$),[10] suggesting a potential mechanism for the improved hyperglycaemia seen in previous animal studies.[29]
- Activation of the CB-1 receptor in liver and adipose tissue in mice increased the expression of genes involved in fat metabolism and fatty acid synthesis.[9] Treatment with rimonabant decreased the expression of these genes, and attenuated the increased rate of hepatic fatty acid synthesis seen with CB-1 activation.[9]
- Rimonabant also increased oxygen consumption in obese mice, suggesting that activation of thermogenesis may contribute to weight loss observed with rimonabant treatment.[10]

2. Pharmacokinetic Profile

Only limited published data on the pharmacokinetics of orally administered rimonabant are available. Data in this section are derived from the manufacturer's prescribing information[30] and conference abstracts.[31-38]

- At doses ≤20mg, rimonabant pharmacokinetic parameters were dose proportional; however, at doses >20mg the increase in area under the plasma drug concentration-time curve (AUC) values was less than dose proportional.[33]
- Following administration of rimonabant 20mg once daily for 21 days to fasted healthy volunteers, a mean steady-state maximum plasma drug concentration (C_{max}) of 196 ng/mL was achieved in ≈2 hours.[33] Mean steady-state parameters (AUC from 0 to 24 hours [AUC_{24}] 2960 ng • h/mL and plasma trough concentration [C_{trough}] 91.6 ng/mL) were achieved within 13 days, and were 3.3-fold higher than those after the first dose.[30,33]
- Following administration with a high-fat meal, rimonabant C_{max} and AUC values were increased by 67% and 48% in comparison with administration in the fasted state.[30]
- In an analysis combining data from seven phase I trials in 141 young healthy volunteers (BMI 18–42 mg/m^2), rimonabant population pharmacokinetics were best described by a two-compartment model for clearance and volume parameters, with a first-order absorption rate constant and lag time.[32]
- Over a wide rimonabant concentration range *in vitro*, human plasma protein binding is >99.9% and is nonsaturable.[30]
- Rimonabant is metabolised by cytochrome P450 (CYP) 3A and amidohydrolase pathways *in vitro*, and circulating metabolites do not contribute to its pharmacological activity.[30]
- Rimonabant is eliminated predominantly through biliary excretion into the faeces (≈86%) as un-

changed drug and metabolites; only ≈3% is eliminated in the urine.[30]

In Obese and Other Special Populations

- BMI appeared to be a major determinant of pharmacokinetic parameters of rimonabant in a population analysis of data from phase I studies, with a significant association between BMI and volume of distribution, reflecting extensive distribution in peripheral tissues.[32]
- Population pharmacokinetic analyses also suggest that fluctuations in peak-to-trough plasma rimonabant concentration are reduced as bodyweight is increased, but steady-state AUC is unaffected.[30] An increase in bodyweight from 65 to 200kg is predicted to reduce C_{max} by 24% and increase C_{trough} by 5%. The time required to achieve steady state was longer (25 days) in obese patients as a result of increased volume of distribution.[33]
- A mean C_{max} value of 188 ng/mL was achieved in ≈2 hours following multiple doses of rimonabant 20mg once daily in healthy obese patients in one study;[33] mean AUC_{24} was 2480 ng • h/mL in the same patient group.[33]
- In obese patients, the elimination half-life ($t_{1/2}$) of rimonabant was longer than in nonobese volunteers (≈16 vs ≈9 days);[33] these differences were attributed to a larger peripheral volume of distribution in obese patients.
- The $t_{1/2}$ of rimonabant was shorter in healthy Japanese volunteers than in Caucasians (3–4 vs ≈9 days).[30] These differences were attributed to disparities in volume of distribution as a result of differences in bodyweight.[30]
- Patients of African descent may have reduced rimonabant C_{max} (up to 31%) and AUC (up to 43%) values in comparison with Caucasians because of increased clearance, decreasing the efficacy of rimonabant in these patients.[30]
- Based on population pharmacokinetics analyses, elderly patients may have higher exposure than young patients (21% higher C_{max} and 27% higher AUC in patients aged 75 vs 40 years).[30] Rimonabant should be used with caution in patients aged >75 years because of lack of sufficient efficacy and safety data.[30]
- Mild renal and hepatic impairment do not seem to affect rimonabant pharmacokinetics, but limited data suggest a 40% increase in exposure with moderate renal impairment.[30] There are no data available for patients with severe renal or hepatic impairment, but it is recommended that rimonabant should not be used in these patients.[30]

Potential Drug Interactions

- Rimonabant AUC was increased by 104% when concomitantly administered with ketoconazole; caution is therefore advised when administering rimonabant in combination with ketoconazole or other potent CYP3A4 inhibitors (e.g. itraconazole, ritonavir, telithromycin, clarithromycin, nefazodone).[30]
- Coadministration of rimonabant and CYP3A4 inducers (e.g. rifampicin, phenytoin, phenobarbital, carbamazepine, St John's wort [hypericum]) has not been examined, but may reduce exposure to rimonabant.[30]
- Rimonabant administration does not affect the pharmacokinetics of digoxin,[35] oral contraceptives,[36] midazolam[38] or nicotine.[34] The pharmacokinetics and pharmacodynamics of warfarin are also not affected by coadministration with rimonabant.[37]
- The pharmacokinetics of rimonabant are not affected by coadministration of orlistat.[31]

3. Therapeutic Efficacy

This section focuses on four large, randomised, double-blind, placebo-controlled, multicentre phase III trials, collectively termed the RIO (Rimonabant In Obesity) trials that investigated the efficacy of oral rimonabant 5 or 20mg once daily in overweight and obese patients.[28,39-42] The RIO trials included the 1-year RIO-Lipids (n = 1036)[28] and RIO-Diabetes (n = 1047)[42] trials and the 2-year RIO-Europe (RIO-EU; n = 1508)[14,39,40] and RIO-North America (RIO-NA; n = 3045)[41] trials. In year 2 of the RIO-NA trial, patients taking rimonabant were re-randomised to receive either placebo or the same

rimonabant dosage (patients receiving placebo continued to receive placebo).[41]

Patients were put on a mildly hypocaloric diet and randomisation was preceded by a 4-week, single-blind, placebo run-in period. Some results are available as an oral presentation.[39]

Inclusion criteria included a baseline BMI of 28–40 kg/m^2,[28,42] or either ≥30 or >27 kg/m^2 plus treated or untreated dyslipidaemia and/or hypertension.[40,41] In the RIO-Lipids trial, patients had untreated dyslipidaemia (fasting TG levels of 1.69–7.90 mmol/L and a ratio of total cholesterol to high-density lipoprotein-cholesterol [HDL-C] of >4.5 for women and >5.0 for men).[28] In the RIO-Diabetes trial, patients had treated type 2 diabetes (HbA_{1c} 6.5–10%, fasting glucose 5.6–15.0 mmol/L and monotherapy with either metformin or a sulfonylurea for ≥6 months, with a stable dosage for ≥3 months).[42] Patients with type 1 or 2 diabetes were excluded from the other three trials.[28,40,41]

Mean values for age, baseline weight and BMI were 45–56 years, 93–105kg and 34–38 kg/m^2.[28,40-42] Where stated, 28–44%[40,41] and 59–64%[42] of patients had hypertension. Excluding the RIO-Lipids trial, 53–64% of patients had dyslipidaemia.[40-42] At baseline, the criteria for the metabolic syndrome (National Cholesterol Education Program Adult Treatment Panel III [NCEP ATP III] criteria: high waist circumference, increased BP and TG levels, low HDL-C levels and impaired glycaemic control)[43] was fulfilled by 32–42% of patients in the RIO-EU and RIO-NA trials,[40,41] and by 52–80% of participants in the RIO-Lipids and RIO-Diabetes trials.[28,42] In the RIO-Diabetes trial, mean baseline HbA_{1c} was 7.3%.[42]

Rates of completion, where stated, were 51–68% during year 1[28,40-42] and 69–77% during year 2.[41]

The primary endpoint for all trials was weight change at 1 year.[28,40-42] Other endpoints included changes from baseline in weight at 2 years, waist circumference, lipid profiles, glycaemic control and/or metabolic syndrome prevalence.

Results presented in this section focus on the approved oral dosage of rimonabant (20mg once daily) and, unless otherwise stated, are those calculated using the last-observation-carried-forward method in the intent-to-treat population.

Weight Loss and Maintenance

- In overweight or obese patients, rimonabant reduced weight to a significantly greater extent than placebo (figure 1a).[28,40-42] At 1 year, mean weight loss was significantly greater with rimonabant 20mg once daily than with placebo in the RIO-EU,[40] RIO-NA,[41] RIO-Lipids[28] and RIO-Diabetes[42] trials (all $p < 0.001$). Rimonabant recipients without type 2 diabetes lost 6.3–6.9kg, whereas placebo recipients lost 1.5–1.8kg;[28,40,41] patients with type 2 diabetes lost 5.3 and 1.4kg after 1 year of treatment with rimonabant or placebo[42] (figure 1a).
- Maintenance of weight loss occurred when rimonabant 20mg once daily was continued for 2 years.[39,41] In the RIO-NA study,[41] patients receiving rimonabant during year 1 who were re-randomised to a second year of rimonabant maintained a 3.6kg placebo-adjusted loss from baseline at the end of the 2-year study period, whereas those re-randomised to placebo regained most of the weight lost ($p < 0.001$). In the 2-year completer population of the RIO-EU study,[39] total weight loss was greater with rimonabant than with placebo (7.2 vs 2.5kg; $p < 0.001$).
- The proportion of obese or overweight patients achieving a weight loss of ≥5% or ≥10% of their baseline weight after 1 year was significantly ($p < 0.001$) greater with rimonabant than with placebo in all four trials (figures 1b and 1c).[28,40-42]
- Where stated, weight loss of ≥5% or ≥10% of baseline continued to be significantly ($p < 0.001$) greater with rimonabant than placebo after 2 years (≥5%: 40% vs 19%[41] [values not reported in RIO-EU];[39] ≥10%: 17% vs 8%[41] and 32% vs 11% [RIO-EU completer population][39]).
- Mean decreases from baseline in waist circumference were significantly ($p < 0.001$) greater with rimonabant 20mg once daily than with placebo at 1 year in the RIO-EU (6.5 vs 2.4cm),[40] RIO-NA (6.1 vs 2.5cm),[41] RIO-Lipids (7.1 vs 2.4cm)[28] and RIO-Diabetes (5.2 vs 1.9cm)[42] trials.

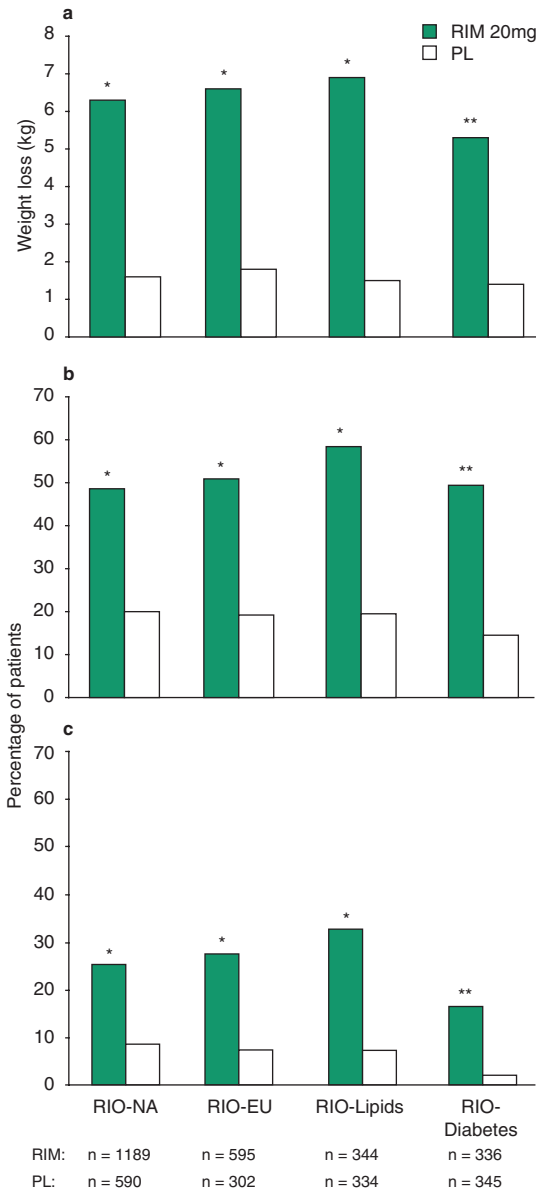


Fig. 1. Efficacy of rimonabant (RIM) in obese or overweight patients. Weight loss in recipients of RIM 20mg once daily (od) or placebo (PL) after 1 year of treatment in the randomised, double-blind, multicentre RIO trials (RIO-NA,[41] RIO-EU,[40] RIO-Lipids[28] and RIO-Diabetes[42]). (**a**) Absolute weight loss from baseline and proportion of patients who lost (**b**) ≥5% or (**c**) ≥10% of baseline weight. Patient numbers are the population with both baseline and post-baseline data. All trials included a RIM 5mg od treatment group (data not shown). * $p < 0.001$, ** $p < 0.0001$ vs PL.

- The overall reduction in waist circumference remained significantly ($p < 0.001$) greater in rimonabant compared with placebo recipients after 2 years of treatment (5.0 vs 2.2cm[41] and 7.5 vs 3.4cm [completer population][39]).

Cardiometabolic Risk Factors

- Rimonabant generally improved the cardiometabolic profile (i.e. glycaemic control, lipid levels and metabolic syndrome prevalence) in obese or overweight patients to a significantly greater degree than placebo.[28,39-42]
- Rimonabant significantly improved glycaemic control compared with placebo in obese or overweight patients.[28,39-42] In the RIO-Diabetes study, statistically significant improvements from baseline were seen in HbA_{1c} values in rimonabant recipients compared with placebo recipients (figure 2a).[42] The effect of rimonabant on HbA_{1c} levels was not entirely attributable to weight loss alone; ≈57% of the change was determined to be independent of the effect of weight loss.[42]
- A significantly greater percentage of patients receiving rimonabant in the RIO-Diabetes study achieved the clinically significant endpoint of HbA_{1c} <6.5% than those receiving placebo (42.9% vs 20.8%; $p < 0.001$);[42] 67.9% of rimonabant recipients achieved a HbA_{1c} level <7.0%, compared with 47.6% of placebo recipients ($p < 0.001$).[14]
- Patients without type 2 diabetes also had improved glycaemic control parameters after rimonabant treatment.[28,40,41] Compared with placebo, rimonabant 20mg once daily for 1 year significantly ($p < 0.05$) improved fasting insulin levels[28,40,41] and/or insulin resistance.[40,41] Fasting plasma glucose levels improved from baseline in rimonabant recipients in the RIO-EU,[40] RIO-NA[41] and RIO-Lipids[28] trials, but the improvements with rimonabant versus placebo were statistically significant in the RIO-EU trial only ($p = 0.026$).[40]
- Improvements in HDL-C levels from baseline were significantly ($p < 0.001$) greater in rimonabant than in placebo recipients in RIO-EU (22.3% vs 13.4%),[14] RIO-Lipids (19.1% vs 11.0%)[28] and RIO-Diabetes (15.4% vs 7.1%)[42] after 1 year of

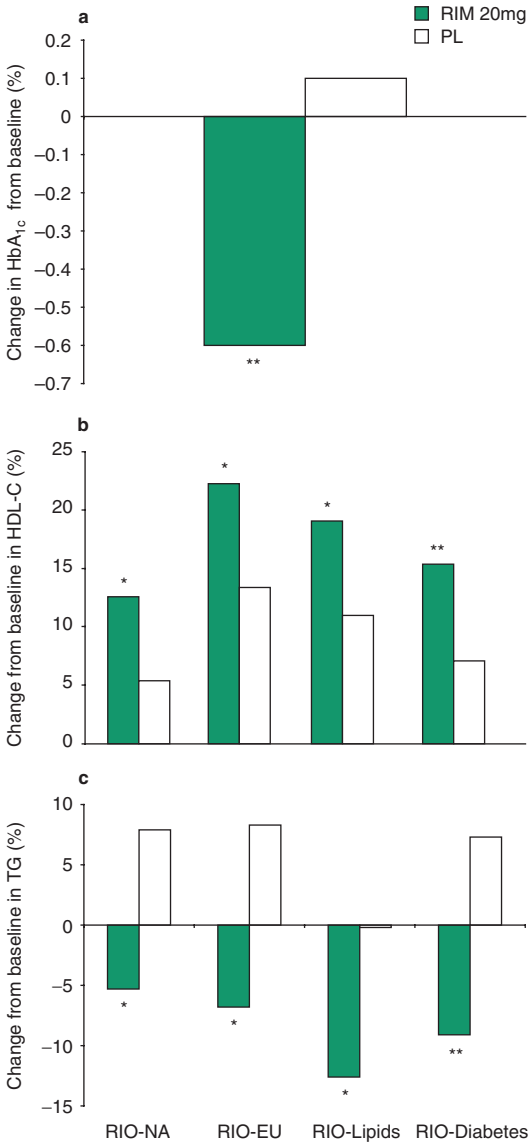


Fig. 2. Efficacy of rimonabant (RIM) in improving glycaemic control and lipid profile in obese or overweight patients. (**a**) Change in glycosylated haemoglobin (HbA_{1c}) in patients with type 2 diabetes mellitus receiving RIM 20mg once daily (od) or placebo (PL) in the RIO-Diabetes study[42]; (**b**) change in high-density lipoprotein-cholesterol (HDL-C) from baseline after 1 year of RIM 20mg od or PL treatment in the randomised, double-blind, multicentre RIO-NA,[41] RIO-EU,[40] RIO-Lipids[28] and RIO-Diabetes[42] trials; and (**c**) change in triglycerides (TG) from baseline after 1 year of RIM 20mg od or PL treatment in RIO-NA,[41] RIO-EU,[40] RIO-Lipids[28] and RIO-Diabetes.[42] All trials included a RIM 5mg od treatment group (data not shown). * $p < 0.001$, ** $p < 0.0001$ vs PL.

treatment (figure 2b). Rimonabant treatment also significantly improved HDL-C levels after the same treatment period in RIO-NA (rimonabant vs placebo: 12.6% vs 5.4%; $p < 0.001$) [figure 2b];[41] this improvement was found to be partially independent of weight loss (58% weight independent).

- HDL-C levels increased with rimonabant treatment by 14.1% (vs 7.8% with placebo)[14] and 22.6% (vs 12.6% with placebo)[39] after 2 years in RIO-NA[41] and RIO-EU[39] (both $p < 0.001$ vs placebo); 57% of the effect of rimonabant on HDL-C levels was found to be independent of weight loss after 2 years of treatment in RIO-EU.[39]

- TG levels were similarly improved with 1 year of rimonabant treatment in all four trials (figure 2c).[28,40-42] A change in TG levels in rimonabant recipients of −5.3% was seen in RIO-NA (vs +7.9% with placebo; $p < 0.001$), with 47% of the change in TG levels at 1 year determined to be weight independent.[41] TG levels were also significantly ($p < 0.001$) improved from baseline in rimonabant recipients compared with placebo recipients in RIO-EU (−6.8% vs +8.3%),[14] RIO-Lipids (−12.6% vs −0.2%)[28] and RIO-Diabetes (−9.1% vs +7.3%).[42]

- TG levels continued to be significantly improved in patients receiving rimonabant 20mg compared with placebo recipients after 2 years of treatment in both RIO-NA[41] and RIO-EU[39] ($p < 0.001$ vs placebo), and the effect was shown to be partially independent of the effect of weight loss in RIO-EU (56% weight independent after 2 years).[39]

- Significant ($p < 0.05$) decreases from baseline in systolic BP in rimonabant compared with placebo recipients were seen in RIO-Lipids (−2.1 vs −0.3mm Hg; $p = 0.048$)[28] and RIO-Diabetes (−0.8 vs +1.6mm Hg; $p = 0.02$)[42] after 1 year of treatment. Diastolic BP was also significantly improved in rimonabant recipients in RIO-Lipids (−1.7 vs −0.2mm Hg; $p = 0.011$ vs placebo).[28] No significant changes in BP in rimonabant recipients were seen in RIO-NA or RIO-EU at 1 or 2 years.[39-41]

- Pooled analysis of all four RIO trials showed that after 1 year of treatment there were significant decreases in both systolic and diastolic BP compared with placebo.[44] The mean change from baseline in

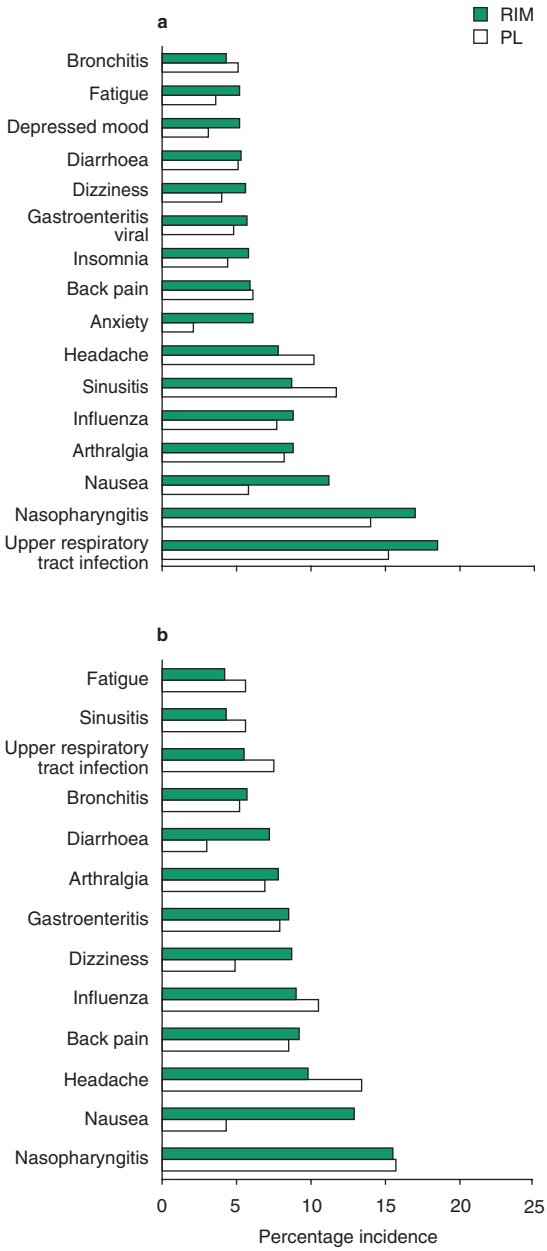


Fig. 3. Tolerability of rimonabant (RIM) in obese patients or overweight patients with associated comorbidities. Adverse events occurring in ≥5% of any treatment group after 1 year of treatment in two randomised, double-blind, placebo (PL)-controlled, multicentre phase III studies: (**a**) RIO-NA (n = 3045)[41] and (**b**) RIO-EU (n = 1508).[14,39,40] Adverse events shown for RIO-NA and RIO-EU are all events reported. Descriptive analyses only were reported.

systolic BP in rimonabant 20mg and placebo recipients was −0.8 and +0.3mm Hg (p = 0.007). Diastolic BP was decreased from baseline −0.8mm Hg in rimonabant 20mg recipients and −0.3mm Hg in placebo recipients (p = 0.029).[44]

- Rimonabant treatment decreased the prevalence of the metabolic syndrome in obese or overweight patients.[28,39,41,42] At 1 year, the proportion of patients fulfilling the NCEP ATP III criteria[43] for the metabolic syndrome in all four RIO trials was significantly ($p \leq 0.007$) lower in rimonabant than placebo recipients.[28,39,41,42] After 2 years of rimonabant treatment, the prevalence of the metabolic syndrome in rimonabant recipients remained significantly ($p < 0.001$) lower than the corresponding percentage in the placebo group.[39,41]

4. Tolerability

- The most common adverse events reported in ≥5% of any treatment group in all four RIO trials are shown in figures 3 and 4. The most common treatment-emergent adverse events that were reported in pooled descriptive data from the trials were upper respiratory tract infection and nausea, with a frequency of ≥10%.[30]
- Where stated, the majority of adverse events were mild to moderate in severity.[28,40-42] The proportion of serious adverse events reported after 1 year in the rimonabant 20mg once daily and placebo groups were 8.7% versus 7.5% (RIO-EU),[40] 4.5% versus 3.5% (RIO-NA),[41] 4.0% versus 2.3% (RIO-Lipids)[28] and 8.0% versus 4.0% (RIO-Diabetes).[42]
- The proportion of discontinuations due to treatment-emergent adverse events during the first year of treatment was numerically higher in the rimonabant than the placebo groups in the RIO-EU (14.5% vs 9.2%),[40] RIO-NA (12.8% vs 7.2%),[14] RIO-Lipids (15.0% vs 7.0%)[14] and RIO-Diabetes (15.0% vs 5.5%)[42] trials.
- The most common adverse events resulting in discontinuation from the studies in a pooled analysis were depressive disorders, anxiety, mood alterations with depressive symptoms, nausea and dizziness.[30]
- Depressive disorders are common in patients being treated for obesity; pooled analysis of the RIO

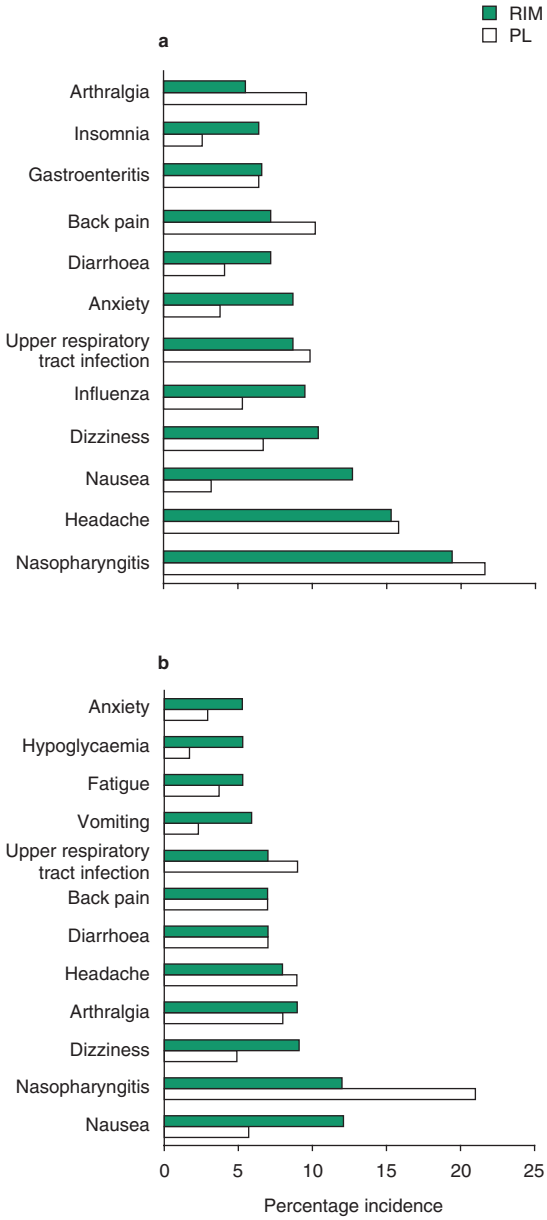


Fig. 4. Tolerability of rimonabant (RIM) in obese patients or overweight patients with associated comorbidities. Adverse events occurring in ≥5% of any treatment group after 1 year of treatment in two randomised, double-blind, placebo (PL)-controlled, multicentre phase III studies: (**a**) RIO-Lipids (n = 1036)[28] and (**b**) RIO-Diabetes (n = 1047).[42] Adverse events shown for RIO-Lipids and RIO-Diabetes are those considered treatment-emergent. Descriptive analyses only were reported.

trials showed that depressive disorders were reported in 3.2% of rimonabant 20mg recipients, compared with 1.6% of placebo recipients.[14,30] These were generally mild or moderate in severity, and all patients recovered after discontinuation of rimonabant therapy or additional corrective treatment.[14,30]

- Pooled data from all four trials showed four deaths in the rimonabant 20mg group and four deaths in the placebo group (one during the placebo run-in period[14]); three deaths were also reported in the rimonabant 5mg group. No deaths were attributed to the study drug.[14]

5. Dosage and Administration

In obese adult patients (BMI ≥30 kg/m^2) or adult patients considered overweight (BMI ≥27 kg/m^2) with associated risk factor(s) such as type 2 diabetes or dyslipidaemia, the recommended dosage of oral rimonabant is 20mg once daily before breakfast. Pharmacotherapy with rimonabant should be undertaken in conjunction with a mildly hypocaloric diet.

Since there is limited data available on the safety of rimonabant in patients with serious uncontrolled psychiatric illnesses, such as major depression, or in patients on antidepressant medication, the use of rimonabant is not recommended in these patients. Local prescribing information should be consulted for further information on special precautions and contraindications related to use of rimonabant.

6. Rimonabant: Current Status

Rimonabant is approved in Europe as an adjunct to a reduced calorie diet and increased exercise for the treatment of obese adults or overweight adults with concomitant risk factors or diseases such as type 2 diabetes or dyslipidaemia.[30] In phase III trials, rimonabant accelerated weight loss in obese or overweight patients with or without type 2 diabetes and/or dyslipidaemia, and improved cardiometabolic risk factors, such as HbA_{1c}, HDL-C and TG levels, beyond that expected for weight loss alone. Rimonabant was generally well tolerated.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

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