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Product name: **Acomplia**
Procedure No: **EMEA/H/C/666/II/04**

SCIENTIFIC DISCUSSION

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I. INTRODUCTION

Rimonabant is a selective antagonist of cannabinoid type 1 (CB1) receptor. Rimonabant is the first member of a new class of compounds that target a novel physiological system, the endocannabinoid system (ECS). The endocannabinoid system has been shown to be involved in the central regulation of food intake and the central nervous system (CNS) reward system. CB1 receptors were first found in the brain, and later in several human tissues, including adipocytes.

At the time of the initial Marketing Authorisation Application (MAA), the proposed indications for rimonabant were the management of multiple cardiovascular risk factors, weight management, type 2 diabetes, dyslipidaemia, smoking cessation and maintenance of abstinence. These indications were not acceptable to the CHMP. The final indication accepted by the CHMP is:

"As an adjunct to diet and exercise for the treatment of obese patients (BMI 30 kg/m2), or overweight patients (BMI > 27 kg/m2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia."

In the current variation, the Marketing Authorisation Holder (MAH) applied for an extension of indication to include the treatment of type 2 diabetes patients (T2DM). The MAH proposed the addition of the following new indication:

"Treatment of type 2 diabetes patients, who are overweight (BMI > 27 kg/m^2), as an adjunct to diet and exercise to improve glycaemic control and to reduce weight in combination with metformin or a sulfonylurea when diet plus a single agent do not result in adequate glycaemic control".

2. CLINICAL ASPECTS

2.1 Clinical Efficacy

Two phase III studies (RIO-Diabetes and SERENADE) have been submitted in support of the current application. Both studies have investigated the safety and efficacy of rimonabant 20 mg in type 2 diabetes mellitus (T2DM) patients. Furthermore, the results of a pharmacodynamic clamp study (EFC5745) are included as support.

The RIO-Diabetes study, which was submitted as part of the initial MAA (April 2005), investigated the effects of rimonabant or placebo on body weight when added to metformin or sulphonylurea (SU) in T2DM patients.

SERENADE, which is a newly submitted trial, studied drug-naïve T2DM patients administered rimonabant 20mg or placebo. The primary endpoint was reduction of HbA1c.

The specific difficulty encountered when analysing metabolic effect of any medicinal product with weight reducing effects is the assessment of the potential weight independent effects on metabolic variables. Therefore, when assessing the effect of rimonabant, the portion of the effect due to body weight changes should be eliminated. This was the main issue for discussion during the initial MAA procedure and at that time it was concluded that the weight change independent effects were too small to allow for a specific indication in T2DM patients.

The RIO-Diabetes results showed a reduction of HbA1c. Part of this effect seems to be independent of weight reduction. The size of this weight independent effect is difficult to estimate, but it was considered that the reduction was around 0.37% in the rimonabant group. The analysis is based on the secondary efficacy end-point with the highest priority in the RIO-diabetes study with approximately 300 patients in each treatment group. However, of more importance is the assessment of the total effect in relation to approved alternatives. As an active control arm of this trial is lacking such comparison is difficult to perform.
In RIO-Diabetes the interaction between treatment and body weight loss was significant (p=0.007), and it was considered that this indicated that the effect on HbA1c was not enough weight change

independent. The body weight-loss adjusted difference in HbA1c was –0.4% ($p<0.001$ for 20 mg rimonabant compared to placebo) compared with an unadjusted difference of –0.7% ($p<0.001$).

The results of SERENADE showed that the rimonabant treated patients achieved a lower HbA1c compared to the placebo treated patients. This change was of the same magnitude as the one seen in RIO-Diabetes. The body weight in the rimonabant group changed from 96.6 to 89.9 kg, a reduction of 6.7 kg over six months; in the placebo group the weight changed from 96.0 to 93.2 kg, a difference of 2.8 kg. This difference makes the assessment of the weight independent effect of rimonabant more difficult. It is, however, acknowledged that the effects on HbA1c have been shown, but the magnitude of the weight independent effect is still not fully clarified. Furthermore an arm of this clinical trial with an active comparator is lacking.

In SERENADE no significant interaction between treatment and weight loss was observed. This implies that HbA1c change is homogenous across different categories of weight loss. Weight loss correlates with a decrease in HbA1c ($p<0.0001$) and since weight loss is higher in the rimonabant than in the placebo group, an additional analysis adjusting for weight change effect on HbA1c was performed. The results, without taking into account weight loss, show an effect on HbA1c of -0.51% ($p=0.0002$ for rimonabant compared to placebo). When weight loss is included in the model, the effect on HbA1c is -0.29% ($p=0.0418$). The change in HbA1c is likely to be due to both weight loss and a weight loss independent effect of rimonabant. It could be estimated that approximately 57% of the change in HbA1c is directly due to the effect of rimonabant. This result therefore confirms the result obtained in the RIO-Diabetes study. However, in SERENADE the 95% confidence interval (CI) of the difference compared to placebo was (-0.78, -0.24) with a point estimate of –0.51.

The CHMP acknowledged that the analyses performed by the MAH demonstrated that rimonabant had an effect on HbA1c independent of weight loss. However, the size of this effect remained uncertain. The treatment alternatives in overweight type 2 diabetes patients failing on oral anti-diabetics (OAD) are limited and the weight gain that almost inevitably occurs when these patients are given insulin is a common and important clinical problem. However, a prospective confirmatory trial with rimonabant focusing on patients failing on OAD is lacking.

In April 2007, the CHMP considered that the lack of comparison of rimonabant with an active control was a major objection to approve the new indication for type 2 diabetes. This view was strengthened by the fact that in the new study, SERENADE, the mean placebo subtracted effect of rimonabant on HbA1c was small and the calculated weight independent effect is only a -0.29% reduction in HbA1c. The CHMP also noted that SERENADE was not conducted in the population claimed. Hence, lack of an adequately designed study in patients failing on OAD makes the efficacy assessment as well as deciding rimonabant's place in the treatment of T2DM patients impossible.

In response to this CHMP major objection, the MAH argued that the mean baseline HbA1c value in RIO-Diabetes was 7.3%, which was low in comparison to that seen in pivotal trials for other anti-diabetic agents. In RIO-Diabetes the placebo-subtracted HbA1c treatment effect in the rimonabant 20 mg group took approximately 9 months to fully develop, and was -0.7%.

As per the MAH, the results of a number of other studies imply that the HbA1c treatment effect of rimonabant 20 mg after 9 months of treatment is comparable to those of the other approved anti-diabetic agents. Both RIO-Diabetes and SERENADE had mean baseline HbA1c values that were lower than those of trials that support the labels of a number of anti-diabetic agents.

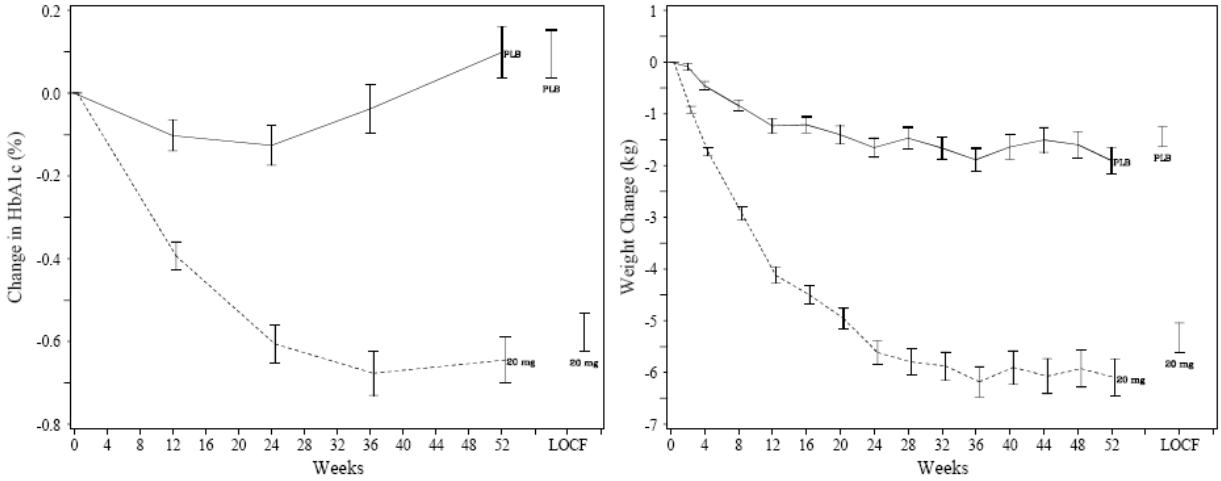
The MAH further argued that the regression analyses performed to determine the magnitude of weight-loss-independent effects on HbA1c in SERENADE and RIO-Diabetes indicated that a similar percentage of the effects in each case (57%) were due to weight-loss-independent effects. According to the MAH this may be because the weight-loss-independent effects of rimonabant develop gradually over time, as do the weight-loss-dependent factors. As per the MAH, it is likely that these non-weight-loss effects would increase in absolute magnitude over the first year of treatment.

In addition, the MAH stated that the body weight and HbA1c changes over the full duration of SERENADE (6 months) and RIO-Diabetes (1 year) were examined in the pooled cohort of 409 RIO-

Diabetes and SERENADE patients (291 placebo and 118 rimonabant 20 mg) with weight changes (increases or decreases) of ≤2.5kg. In these patients, who can be considered as those with stable body weight, the mean reduction in HbA1c associated with rimonabant 20 mg vs placebo was -0.37% ($p<0.0001$). The associated placebo-subtracted weight loss for these patients associated with rimonabant 20mg treatment was -0.5kg.

The changes in mean HbA1c and body weight over time by treatment in RIO-Diabetes (see fig below) indicate that mean HbA1c increased in the placebo group over the last 6 months of the study. The fact that this was observed without a parallel increase in body weight in the placebo group over this period is an indication that it was based on other, non-weight-loss-related factors (eg diabetes progression), and the fact that the same increase in mean HbA1c did not occur in the rimonabant 20mg group over the last 6 months of the trial is an indication that rimonabant 20mg treatment successfully addressed these factors.

Change (%) by visit and LOCF at 1 year (mean change ±SEM), ITT population for HbA1c (left) and body weight change (kg) (right).



The CHMP also objected the lack of trials confirming the effects of rimonabant in diabetic patients failing monotherapy treatment with metformin or sulfonylurea. The MAH argued that when patients from RIO-Diabetes who were treated with maximal or near-maximal doses of metformin or sulfonylurea were analyzed separately in terms of HbA1c treatment effects, the effects of rimonabant 20 mg on HbA1c vs placebo were similar (even better for metformin treated patients) to what they were in the overall population, and the changes vs placebo in HbA1c were statistically (and clinically) significant in both cohorts treated with high doses of background agents, despite the smaller sample size of these cohorts.

Additionally, the CHMP was of the view that the design of the clamp study (EFC5745) did not allow demonstration of any benefit from rimonabant compared to placebo. As the outcome of the study was inconclusive, the CHMP was of the opinion that the study does not support that rimonabant has an intrinsic anti-diabetic effect.

The clamp study was an exploratory, short-term (8 week), placebo controlled study of rimonabant 20 mg vs placebo in 40 (20 per treatment group) non-diabetic insulin-resistant individuals, so defined based on the presence of overweight (BMI 27 to 35 kg/m2), impaired fasting glucose (IFG), and hypertriglyceridemia. It was undertaken by the MAH to attempt to dissociate effects on peripheral insulin sensitivity from changes in body weight and it was not intended to be a pivotal study to support the submission.

The MAH argued that this study was included because it was completed during the period between the initial submission and the variation application, and was discussed because it addressed one of the secondary efficacy parameters of the variation, insulin sensitivity. Its population was not diabetic by design, and because of its defining metabolic abnormality (Impaired Fasting Glucose) it would have been unlikely that any significant response of blood glucose could have been demonstrated.

The MAH recognised that the results of the clamp study are inconclusive; moreover they do not support the conclusion that rimonabant had no intrinsic (i.e. weight-loss-independent) effect on glucose lowering in type 2 diabetic patients.

Conclusion on efficacy

The CHMP acknowledged that there is an effect on glucose metabolism. However, the clinical relevance of the effect observed as well as the magnitude of the weight independent effects has not been established. The total effect on the HbA1c levels appears to be of moderate size. The CHMP and the MAH agreed that the weight independent effect on HbA1c of rimonabant is small. The lack of data from studies including an active control makes an assessment of the observed effects difficult. The CHMP was of the opinion that the SERENADE study provides additional support for the already approved indication but is not sufficient to support the proposed indication.

In conclusion, sufficient data have not been submitted to justify an indication in type 2 diabetes patients. However, since treatment of overweight in patients with type 2 diabetes was already included in the current indication for treatment of overweight patients with additional risk factors, the CHMP agreed that results from the submitted studies could be included in the product information.

2.2 Clinical safety

This section will concentrate on the pooled safety data from RIO-Diabetes and SERENADE. The safety population consisted of all randomised patients who took at least 1 dose of investigational drug irrespective of duration of treatment. Patients were analyzed in the actual treatment group as dispensed at the randomisation visit. Prospectively, in SERENADE all treatment-emergent adverse events (TEAEs) in the nervous system disorder or psychiatric System Organ Class (SOCs) were queried via complementary data queries (CDQs) in response to a regulatory request to obtain additional information on the diagnosis, evaluation, and treatment of such TEAEs. For RIO-Diabetes, CDQs were issued retrospectively for all patients, after the study's conclusion, to gather the same information for AEs in the nervous system or psychiatric SOCs.

Patient exposure

A total of 965 patients were randomized and completed the planned treatment period and exposed to either rimonabant 20 mg (477 patients) or placebo (488 patients) in the 2 studies. The cumulative exposure in patient years was 341.6 patient-years in the placebo group compared to 328.9 patient-years for rimonabant. The mean duration of exposure was similar between the placebo (256 days) and rimonabant (252 days) groups. About one-half of the total number of patients in the rimonabant group had received rimonabant 20 mg for >300 days.

Adverse events (AEs)

There were slightly more TEAEs in the rimonabant group (80.7%; 385 of 477) compared to the placebo group (73.2%; 357 of 488) and a greater number of patients administered rimonabant (13.4%; 64 of 477) discontinued due to TEAEs compared with the placebo group (4.5%; 22 of 488). Among the most frequently reported SOC (≥10% in any group), those in which events were reported more frequently with rimonabant than with placebo were in the psychiatric, nervous system, and gastrointestinal (GI) disorders.

The incidence of TEAEs leading to discontinuation was higher in the rimonabant (13.4%; 64 of 477) group compared with placebo (4.5%; 22 of 488). Among the most frequently reported SOC (≥2% in any group), those in which events were reported more frequently with rimonabant than with placebo were in the psychiatric (rimonabant: 5.2%; placebo: 0.8%), nervous system (rimonabant: 3.1%; placebo: 0.4%), and gastrointestinal (rimonabant: 2.9%; placebo: 0.6%) disorders.

Adverse events of special interest

Mood alterations, depressive symptoms, and anxiety

The incidence of mood alterations and depressive symptoms (includes depressed mood, depressive symptoms and tearfulness) was higher in the rimonabant group (6.1%) than in the placebo (2.7%) group. Analysis of these TEAEs showed slightly higher incidences in the rimonabant group when compared with placebo: depressed mood (rimonabant: 4.2%; placebo: 2.0%), depressive symptoms (rimonabant: 1.9%; placebo: 0.6%), and tearfulness (rimonabant: 0.2%; placebo: 0%). In the rimonabant group, the majority of these events were characterized as mild or moderate. The mood alterations and depressive symptoms were considered related to rimonabant in 2.1% of the patients.

The incidence of anxiety was higher in the rimonabant group (5.2%) than in the placebo (2.9%) group. In the rimonabant group, the majority of these events were characterized as mild. The anxiety was considered related to rimonabant in 1.5% of the patients. Anxiety led to discontinuation in 3 (0.6%) patients. Among the psychiatric symptoms, that were reported more frequently ($\geq$2 patients) in rimonabant treated patient compared to placebo were anxiety disorders (11 patients), melancholic symptom (5 patients), aggressivity (4 patients), suicidal ideation/thought of death (3 patients), and feeling of worthlessness (2 patients).

Nausea and vomiting

The incidence of nausea was higher in the rimonabant group (11.3%) than in the placebo (5.5%) group. The events were mainly characterized as mild or moderate in intensity. The nausea was considered related to rimonabant in 5.5% of the patients. Nausea as a serious adverse event (SAE) led to treatment discontinuation in 8 (1.7%) patients in the rimonabant group.

The incidence of vomiting was higher in the rimonabant group (5.5%) than in the placebo (1.8%) group. The events were mainly characterized as mild or moderate in intensity, with a majority of onset from Day 31-Day 90 after initiation of rimonabant. The vomiting was considered related to rimonabant in 1.3% of the patients. Vomiting led to treatment discontinuation in 3 (0.6%) patients in the rimonabant group.

Dizziness

The incidence of dizziness was higher in the rimonabant group (9.6%) than in the placebo (4.3%) group. The majority of events were characterized as mild. The dizziness was considered related to rimonabant in 3.1% of the patients. Dizziness led to treatment discontinuation in 5 (1.0%) patients in the rimonabant group.

Hypoglycaemia

Hypoglycaemia was reported as a TEAE in a greater number of patients in the rimonabant (4.0%; 19 of 477) group when compared with placebo (1.4%; 7 of 488).

In the RIO-Diabetes study, a blood glucose level of $\leq$2.5 mmol/L was to be reported as an adverse event. Hypoglycaemia was reported with a higher incidence in the rimonabant group (18; 5.3%) compared with the placebo group (6; 1.7%). Hypoglycaemic events were reported more frequently in the rimonabant group (18 cases). In the rimonabant group, 8 patients with TEAEs of hypoglycaemia were treated with biguanides and 10 were treated with sulfonylureas (SU). Seventeen patients with hypoglycaemia in RIO-Diabetes continued rimonabant 20 mg. Their anti-diabetic therapy was reduced in 9 cases, maintained at the same dosage in 7 cases, and switched to another treatment in 1.

In the SERENADE study, symptomatic hypoglycaemic episodes were defined as an event with clinical symptoms considered as resulting from hypoglycaemia. Two patients in the SERENADE study, one in each treatment group, reported single non-serious episodes of mild symptomatic hypoglycaemia.

Paresthesia

Paresthesia was reported as a TEAE in a greater number of patients in the rimonabant (2.9%; 14 of 477) group compared to placebo (0.8%; 4 of 488). A majority of the 14 cases were not considered

related to study drug. Most cases had an atypical body distribution for classical diabetic sensory neuropathy (sparing the lower limbs). Specific information about pre-existing diabetic neuropathy was not collected in either study. Paresthesia as medical history was reported for only one patient in the placebo group, and did not predispose to paresthesias as TEAEs. Six of the 14 patients with TEAEs of paresthesia in the rimonabant group had concomitant medical conditions (i.e. carpal tunnel syndrome, vitamin B12 deficiency, cardiovascular accident (CVA), rheumatoid arthritis) or concomitant medication (anti-epileptic) that could have predisposed them to develop paresthesias. Five of the 14 affected patients in the rimonabant group discontinued treatment.

Serious adverse events and deaths

Serious TEAEs were slightly more frequent in the rimonabant (7.5%; 36 of 477) group compared with placebo (4.1%; 20 of 488). Among the most frequently reported SOC (≥1% in any group), those in which events were reported more frequently with rimonabant than with placebo were in the injury poisoning and procedural complications (rimonabant: 1.5%; placebo: 0.4%), cardiac (rimonabant: 1.9%; placebo: 1.0%), gastrointestinal (rimonabant: 1.0%; placebo: 0.0%), and nervous system disorders (rimonabant: 1.0%; placebo: 0.4%).

In the rimonabant 20 mg group, the most frequently reported serious TEAEs were, road traffic accident (3 patients), hypoglycaemia, coronary artery disease, cardiac failure, cholelithiasis, renal colic, chest pain, fall, and traumatic fracture (2 patients each). All 3 cases of road traffic accident were in the RIO-Diabetes study; 2 of the 3 cases were associated with hypoglycaemia. Of note, in the RIO-Diabetes study all patients were on Oral Anti-diabetics (OADs). In the placebo group, the most frequently reported serious TEAE was cholelithiasis (2 patients).

A total of 5 deaths (3 in the rimonabant 20 mg group, 1 in the rimonabant 5 mg group, and 1 in the placebo group) were reported in the two studies during the treatment period. The investigators excluded a causal relationship to the investigational product for each of these events resulting in death. In the RIO-Diabetes study, there was also 1 death (cardiac arrest) during the placebo run-in period.

Laboratory findings

There were no specific changes in electrocardiographic, chemistry, or haematology parameters for which rimonabant showed an increased incidence over placebo.

Post-marketing data

Rimonabant was approved on late 2006; therefore the post-marketing data is relatively sparse. The AEs from spontaneous reports mirror the ones found in the clinical trials with GI, nervous system disorder, and psychiatric AEs as the more common findings. Symptoms such as nausea, diarrhoea, and hyperhidrosis were the most common individual events reported.

Conclusion on safety

The adverse event profile in the new data is comparable to events previously reported. However, paresthesia is a new event not found before and therefore has been added to section 4.8 of the Summary of Product Characteristics and to the Package Leaflet.

Although the psychiatric adverse events still cause concern, and this concern is enhanced by the present report of three episodes of suicidal ideation, two of these occurred in patients without a prior history of psychiatric illness, it was considered that the product information includes sufficient information on them and the importance of the agreed Risk Management Plan was highlighted.

3. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The RIO-Diabetes study investigated the effects of rimonabant or placebo when added to metformin or SU in T2DM patients on body weight. SERENADE studied drug-naïve T2DM patients administered rimonabant 20mg or placebo, the primary endpoint was reduction HbA1c.

In these studies, rimonabant demonstrates a modest decrease in HbA1c compared to placebo. The extent of decrease in HbA1c that can be attributed to a weight independent effect of rimonabant is undetermined. The difference in HbA1c decrease was estimated to be -0.29 percentage points.

The new data submitted with the application does not expand the knowledge of the contribution of rimonabant in the treatment of T2DM patients. To determine this, studies including a comparison with an active control, especially metformin, are needed. The request for such studies is also supported by current guidelines.

Safety data did not deviate from the results of previously submitted study data. The only new event is paresthesia, which the MAH agreed to add to section 4.8 of the SPC. The concerns regarding psychiatric ADRs remain.

In conclusion, rimonabant has a modest effect on HbA1c, but the clinical relevance is not demonstrated versus an active comparator. Therefore, the benefit-risk assessment for an indication in diabetes type 2 is currently negative. However, since treatment of overweight in patients with type 2 diabetes was already included in the current indication for treatment of overweight patients with additional risk factors, the CHMP agreed that some data on the results of the submitted studies could be included in section 5.1 of the Summary of Products Characteristics.