European Medicines Agency

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ASSESSMENT REPORT
FOR
ACOMPLIA

International Nonproprietary Name:
rimonabant

Procedure No. EMEA/H/C/000666/A20/0012

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE SUSPENSION OF ACOMPLIA PRESENTED BY THE EMEA

Acomplia (rimonabant) is a selective antagonist of cannabinoid type I (CB1) receptors. The cannabinoid 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.

Acomplia was authorised in the EU on 19 June 2006. It is indicated "as an adjunct to diet and exercise for the treatment of obese patients or overweight patients with associated risk factors such as type 2 diabetes mellitus or dyslipidaemia". At the time of approval, a higher incidence of dizziness, anxiety, depressed mood and depressive disorders were observed in the 20 mg rimonabant group, compared with placebo. Risk minimization strategies were included in the product information which have since then been tightened to include contraindications for major depression and use of antidepressant. Additionally, warnings concerning past history of depressive disorder, the need to monitor for the emergence of depressive symptoms or mood alteration and a warning to stop rimonabant if depression is diagnosed have been introduced in the product information.

In the conclusions of PSUR 3 (March 2008) it was noted that the reporting rate for depressive disorders had increased markedly during the last 6-month period compared to the first 1-year period of marketing (24 cases per 10,000 treated patients versus 13). The reporting rates for cases related to suicidality and aggressive behaviour had also increased. These findings raised significant safety concerns regarding rimonabant and the risk of psychiatric disorders. Thus, the MAH was requested to provide further analysis on this topic.

Additional safety concerns arose from the results of the STRADIVARIUS trial (JAMA April, 2008). In this study, the absolute reporting rate of psychiatric adverse events was higher compared to previous studies (43.4% vs 28.4%, $p<0.001$ for rimonabant and placebo, respectively).

At the April 2008 CHMP meeting, the Committee agreed to convene the Scientific Advisory Group (SAG) on Diabetes and Endocrinology to discuss the benefits and risks of rimonabant and its place in therapy.

The SAG meeting was held in June 2008 and the group looked at all of the available data on the benefits and risks of Acomplia. The experts were concerned that the margin of benefits over risks for Acomplia had narrowed since the medicine's approval, but agreed that more data were needed before a conclusion could be reached.

At the July 2008 CHMP meeting, it was considered that there were uncertainties with the benefit/risk of Acomplia and the CHMP requested the MAH to submit further analyses on the above-mentioned safety concerns, the duration of treatment and potential subgroups that may be more likely to respond to the treatment. The overall assessment of these data confirmed the previously safety concerns of Acomplia without identifying any subgroups with a potentially more favourable benefit/risk balance.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the Committee on 20 October 2008 to assess the above concerns and its impact on the risk/benefit balance for Acomplia, and to give its opinion on measures necessary to ensure the safe and effective use of Acomplia and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

The CHMP after reviewing all the available data submitted by the MAH to address the increased concern over the psychiatric adverse events and its impact on the risk benefit-risk concluded the following:

Efficacy

In clinical studies, in which the patients were treated for more than a year, the weight reducing effect of rimonabant was moderate but probably of clinical relevance for 20-30 % of the treated patients. However, since new data have now emerged indicating a shorter duration of treatment in "real life" than what was tested in the clinical trials setting, the benefit of the weight reduction would be more limited with this short-term use of the product. Results from studies finalised after approval point out to the same direction, as they also indicate a more limited effect on weight reduction compared to the initial trials.

Rimonabant has beneficial effects on HDL-cholesterol, triglycerides and HbA1c. This could be advantageous since the prevention of cardiovascular disease should be based on a multi-factorial approach. However, these effects were rather limited and the potential benefits are based on a long term treatment approach. Furthermore the results of the Stradivarius study did not indicate any effect on the progression of atherosclerosis as measured by the IVUS technique.

Safety

Gastrointestinal, nervous and psychiatric disorders have been identified as known side effects of rimonabant treatment. Depression and related problems have been serious concerns since the time of approval and strengthened warnings and contraindications have been added to the product information, along with distribution of DHCP letters.

Data from clinical studies indicate that there is approximately a 1.5- 2 fold increased risk of psychiatric disorders (mainly depressive and sleep disorders and anxiety) associated with the use of rimonabant. This relative risk may not have increased since the time of approval, but the absolute numbers are quite different depending on study population and study design, with higher absolute risks in patients with comorbidities. In addition, the latest analysis provided by the MAH shows that the absolute incidence of clinically severe depressive disorders occurred more commonly.
About 50% of the depressions occurred during the first 3 months of treatment and the main risk factors to develop depressive disorders were concurrent and past history of depressive disorders and co-administration of antidepressants. However, depressive reactions may occur in patients who have no obvious risk factors, apart from obesity itself.

In the finalised clinical studies, the incidence of suicidal ideation was similar between placebo groups and rimonabant with only one completed suicide. However, in ongoing studies 6 additional cases of completed suicide have been reported out of which 5 cases were treated with rimonabant. This is a serious safety concern.

The post-marketing experience confirms the safety profile of rimonabant already observed in clinical trials, with the cases being mostly from psychiatric origin and also indicating an increased risk of aggressiveness which was not seen in clinical trials.

According to prescription surveys, a high adherence is noted for the respect of the indication. However, the adherence to warnings and contraindications may be considerably lower considering that concomitant use of antidepressants in patients prescribed Acomplia is still 6-20 %. This represents a safety concern.

Benefit/Risk Balance

The efficacy of rimonabant as a weight-reducing agent can be considered as moderate. The beneficial effects on cardiovascular risk factors may be of limited importance considering the reported short duration of use. No new subgroups with an expected increased benefit of rimonabant treatment have been identified and patients at an elevated risk of developing psychiatric disorders could not be identified either. The expected benefits are considered as more limited compared to what was foreseen at the time of approval.

The safety profile for rimonabant with a 1.5- 2 fold increased risk of psychiatric disorders, has been shown to translate into high absolute risks in real life situations, especially in patients with comorbidities and patients with previous history of psychiatric disease. The absolute risk of psychiatric adverse event in clinical practice may be more common compared to what was seen at the time of approval. In addition, the suicide cases reported in the ongoing clinical trials are of concern.

Overall Conclusion

Based on the reported short duration of use, and the fact that no subgroups with an expected increased benefit has been identified, it is concluded that the clinical benefit of the treatment with rimonabant are less pronounced compared to the time of approval. Given the generally short duration of treatment the evidence of clinical benefit in the prevention of cardiovascular disease is also lacking.

Based on the higher absolute risks of psychiatric adverse event in clinical practice and the limited impact of risk minimisation activities, the risks of psychiatric adverse events such as depressions, anxiety, sleep disorders and aggressive behaviour are considered as more serious concern compared to the time of approval.

It is unlikely that additional measures to reduce exposure of patients most at risk of psychiatric reactions will lead to a favourable balance of risk and benefit because the patients at highest risk of these reactions, and those that might benefit most from the product, cannot reliably be identified.

Taken this into account, the benefit/risk balance for rimonabant is considered as negative.

GROUNDS FOR SUSPENSION PRESENTED BY THE EMEA

The Committee reviewed all available information on the benefits and risks of Acomplia including all studies that have been completed and post-marketing data available.

The Committee considered that in clinical studies in which the patients were treated for more than a year, the weight reducing effect of Acomplia was moderate and of clinical relevance for 20-30 % of the treated patients as reflected by the 10 % responder rate.

The Committee considered that Acomplia also has moderate beneficial effects on HDL-cholesterol, triglycerides and HbA1c. However, since available data indicate that patients only take Acomplia for short periods, there is currently no evidence of Acomplia preventing cardiovascular disease.

The Committee considered that the new data from clinical studies and post-marketing reports showed that in clinical practice the psychiatric disorders such as depressions, anxiety, sleep disorders and aggressive behaviour are more common compared to what was seen at the time of approval. In addition, the suicide cases reported in the ongoing clinical trials are of serious concern.

The Committee concluded, in view of available data, that the risks associated with the use of Acomplia as an adjunct to diet and exercise for the treatment of obese or overweight patients with risk

factors such as type 2 diabetes or dyslipidaemia outweigh the benefits. In addition, the Committee considered that the current and proposed risk minimisation activities were not adequate to reduce the risks to an acceptable level or predict which patients may be at risk.

The Committee, as a consequence, concluded that the benefit/risk balance of Acomplia is not positive under normal conditions of use.

The CHMP has therefore recommended the suspension of the Marketing Authorisation for Acomplia.

The CHMP also recommended that provisional measures are needed and therefore recommends to the European Commission that the marketing of Acomplia be suspended in all concerned EU Member States awaiting the adoption of the Commission Decision.