

DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION

Prescribers should not issue or renew any prescription for ACOMPLIA

Patients who are currently taking ACOMPLIA should consult their doctor or pharmacist at a convenient time to discuss their treatment.

Sanofi-aventis would like to inform you that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended the suspension of the marketing authorisation for Acomplia (rimonabant). In line with this recommendation, Sanofi- Aventis is requesting you to not prescribe or dispense Acomplia.

Acomplia has been authorised in the EU since June 2006 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 and dyslipidaemia.

At the time of approval, warnings of psychiatric side effects, in particular depression, were included in the product information, and identified as the main area for further monitoring. There was approximately a doubling of the risk of psychiatric disorders in patients taking Acomplia in completed clinical studies versus placebo. The product information has been continuously updated and strengthened to include further contraindications and upgraded warnings on these concerns to manage the risks associated with the use of Acomplia.

Following the assessment of the available information on the benefits and risks of Acomplia, the CHMP at its October 2008 meeting, considered that in clinical practice the serious psychiatric disorders such as depression, anxiety, sleep disorders and aggressiveness may be more common compared to what was foreseen at the time of approval. Furthermore, the CHMP was concerned that depression could lead to suicidal ideation or even suicide attempts.

In line with the recommendation of the EMA:

Information for the prescriber:

- Do not issue or renew any prescription for ACOMPLIA,
- Patients currently included in clinical trials with Acomplia should be invited to contact their investigator at a convenient time.
- There is no need for patients to stop treatment with Acomplia immediately, but patients who wish to stop can do so at any time.

Information for the pharmacist:

- Do not dispense any additional package of Acomplia to patients
- Patients who are currently taking Acomplia should be invited to consult their doctor at a convenient time to discuss their treatment.

- There is no need for patients to stop treatment with Acomplia immediately, but patients who wish to stop can do so at any time.

Call for reporting

Healthcare professionals should report any adverse event suspected to be associated with the use of Acomplia to the Medicines and Healthcare products Regulatory Agency using a Yellow Card available directly from the MHRA, CHM Freepost, London SW8 5BR, or electronically via the MHRA website (www.yellowcard.gov.uk).

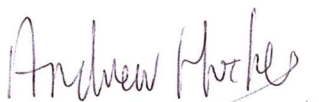
Communication information

Please contact sanofi-aventis if you have any additional questions.

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We remain at your disposal for any further information you may need.

Yours sincerely,



Dr Andrew Hockey
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Annexes:

Text of the EMEA Press Release and Q&A



EMBARGO
DO NOT PUBLISH BEFORE 23 OCTOBER 2008, 16.00hrs (UK time)

PRESS RELEASE

The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia

The European Medicines Agency (EMA) has recommended the suspension of the marketing authorisation for Acomplia (rimonabant) from Sanofi-Aventis. The EMA's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Acomplia no longer outweigh its risks and the marketing authorisation should be suspended across the European Union (EU).

Acomplia has been authorised in the EU since June 2006 as an adjunct to diet and exercise for the treatment of obese patients or overweight patients with associated risk factors. Warnings about psychiatric side effects, in particular depression, have been included in the product information since Acomplia was first authorised. The product information for Acomplia has been continuously updated and strengthened to include further contraindications and upgraded warnings on these concerns to manage the risks associated with the use of Acomplia.

Following the assessment of the available information on the benefits and risks of Acomplia including data from studies completed since it was granted marketing authorisation, the CHMP confirmed at its 20-23 October meeting, that there is an approximate doubling of the risk of psychiatric disorders in obese or overweight patients taking Acomplia compared to those taking placebo.

The CHMP considered that the new data from post-marketing experience and ongoing clinical trials indicated that serious psychiatric disorders may be more common than in the clinical trials used in the initial assessment of the medicine. The CHMP was also of the opinion that these psychiatric side effects could not be adequately addressed by further risk minimisation measures.

In addition, the CHMP noted, that the effectiveness of Acomplia in clinical practice is more limited than was expected on the basis of the clinical trials, because available data indicate that patients generally take Acomplia only for a short period.

Prescribers should not issue any prescriptions for Acomplia and should review the treatment of patients currently taking the medicine. Patients who are currently taking Acomplia should consult their doctor or pharmacist at a convenient time to discuss their treatment. There is no need for patients to stop treatment with Acomplia immediately, but patients who wish to stop can do so at any time. Patients currently included in clinical trials with Acomplia should contact the investigator, who will be able to provide more information.

The CHMP opinion will now be sent to the European Commission for the adoption of a decision, applicable in all EU countries.

-- ENDS --

Notes:

1. More information is available in a question-and-answer document.

2. The suspension of a marketing authorisation is a precautionary measure, during which time a medicinal product is not available. The lifting of the suspension is conditional on the marketing authorisation holder resolving the issues identified by the Agency
3. Acomplia is marketed in 18 Member States (Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Lithuania, Malta, the Netherlands, Slovakia, Spain, Sweden and the United Kingdom). Rimonabant is also authorised as Zimulti. Zimulti is not marketed in the EU.
4. In July 2007, the CHMP recommended contraindicating Acomplia in patients with ongoing major depression or who are being treated with antidepressants. Furthermore, in May 2008, the CHMP recommended updating the product information to reflect the fact that depression may occur as a side effect of Acomplia in patients who have no obvious risk factors apart from obesity itself, and to advise prescribers to monitor patients for signs and symptoms of psychiatric disorders, particularly depression, after the start of treatment.
5. The review of Acomplia was initiated under Article 20 of Regulation (EC) No 726/2004. This type of procedure is initiated when there are public health concerns with a centrally authorised medicine. The European Commission asked the CHMP to assess all aspects of safety of the centrally authorised medicines containing rimonabant and to give its opinion on the measures deemed necessary to ensure the safe use of rimonabant and on whether the marketing authorisation for these products should be maintained, varied, suspended or withdrawn.
6. More information on Acomplia is available in the European Public Assessment Report (EPAR) on the Agency's website:
<http://www.emea.europa.eu/humandocs/Humans/EPAR/acomplia/acomplia.htm>
7. This press release, together with other information on the work of the EMEA, can be found on the EMEA website: www.emea.europa.eu

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DO NOT PUBLISH BEFORE 23 OCTOBER 2008, 16.00hrs (UK time)

Questions and answers on the recommendation to suspend the marketing authorisation of Acomplia (rimonabant)

The European Medicines Agency (EMA) has completed a review of Acomplia (rimonabant) at the request of the European Commission, following concerns over the medicine's psychiatric safety. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of Acomplia no longer outweigh its risks, and that its marketing authorisation should be suspended across the European Union (EU). The review was carried out under an 'Article 20' referral¹.

What is Acomplia?

Acomplia is a medicine containing the active substance rimonabant. It is used together with diet and exercise to reduce weight in adult patients who are:

- obese (very overweight) with a body mass index (BMI) greater or equal to 30 kg/m², or;
- overweight (BMI greater or equal to 27 kg/m²) and also have other risk factors, such as type 2 diabetes or dyslipidaemia (abnormal levels of fat in their blood).

The active substance in Acomplia, rimonabant, is a cannabinoid receptor antagonist. It acts by blocking a specific type of receptor called cannabinoid type 1 (CB1) receptors that are found in the nervous system and are part of the system that the body uses to control food intake. By blocking the receptors, rimonabant can help patients to reduce food intake and to lose weight. The receptors are also found in adipocytes (fat cells).

Acomplia has been authorised in the European Union since June 2006 and is marketed in 18 EU Member States². Rimonabant is also authorised as Zimulti, but this product is not marketed in the EU.

What is the issue with Acomplia?

The CHMP has been aware that Acomplia can cause psychiatric side effects, especially depression, since its initial assessment. Warnings about psychiatric safety have been included in Acomplia's product information since its first authorisation. Since then, the CHMP has been monitoring the medicine closely and changes to the product information have been introduced as new data have become available.

The ongoing review of the medicine led to the CHMP's recommendation in July 2007 to restrict the medicine's use. This resulted in the addition of a contraindication for patients with ongoing major depression or taking antidepressants. A warning was also added to the prescribing information, stating that treatment with Acomplia should be stopped if a patient develops depression³.

¹ Article 20 of Regulation (EC) No 726/2004.

² Acomplia is marketed in Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Germany, Greece, Ireland, Italy, Lithuania, Malta, the Netherlands, Slovakia, Spain, Sweden and the United Kingdom.

³ For more information on this recommendation, see the question-and-answer document [here](#).

The CHMP recommended a further update in May 2008 to reflect new information on psychiatric reactions and to advise prescribers to monitor patients for signs and symptoms of psychiatric disorders, particularly depression, after the start of treatment.

Because of new data showing increasing concern over the psychiatric safety of Acomplia, the CHMP decided to ask a group of experts in diabetes, cardiovascular disease and psychiatry to review the medicine. The group met in June 2008, and 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.

As the assessment of the latest data from the company continued to raise concerns over the safety of Acomplia, the European Commission issued a formal request under Article 20 of Regulation (EC) 726/2004. This enabled the CHMP to prepare an opinion on whether the marketing authorisation for Acomplia should be maintained, changed, suspended or withdrawn across the EU.

Which data has the CHMP reviewed?

This review included all available information on the benefits and risks of Acomplia, focusing on its psychiatric side effects in patients taking the medicine, including new information that had become available after the expert meeting in June 2008. The information came both from the company's monitoring of the use of the medicine from its launch until September 2008, and from studies conducted by the company that have been completed since Acomplia was granted marketing authorisation.

What were the conclusions of the CHMP?

The CHMP confirmed that Acomplia is moderately effective in helping patients to lose weight. It also confirmed that the medicine has some benefits in terms of its effects on blood fats and blood glucose control. However, the new data show that in real life, patients tend to stop their treatment early. This short-term treatment with Acomplia may not bring the benefits expected on the basis of the clinical trials. There is also no evidence that Acomplia prevents cardiovascular disease (disease of the heart and blood vessels).

The Committee confirmed that the risk of psychiatric side effects, including depression, sleep disorders, anxiety and aggression, is approximately doubled in patients taking Acomplia, compared to obese or overweight taking placebo (a dummy treatment). The new data from ongoing studies and post-marketing reports indicated that serious psychiatric disorders may be more common than in the clinical trials used in the initial assessment of the medicine.

Since the medicine has been on the market, an increasing number of cases of serious psychiatric disorders, including suicide, have been reported. In addition, between June and August 2008, five cases of suicide were reported in patients taking Acomplia in ongoing studies, compared with one case in patients taking placebo. These were seen in a total of around 36,000 patients. The Committee was also concerned that some patients taking antidepressants were still being prescribed Acomplia despite the introduction of the contraindication for these patients in 2007.

Because patients at an elevated risk of developing psychiatric disorders could not be identified, the Committee concluded that introducing further restrictions to the use of the medicine would be unlikely to reduce the risk to an acceptable level. Therefore, the Committee concluded that the benefits of Acomplia no longer outweigh its risks, and recommended that the marketing authorisation for the medicine should be suspended across the EU.

What is the advice to patients and prescribers?

- Prescribers should not issue any prescriptions for Acomplia and should review the treatment of patients currently taking the medicine.
- Patients who are currently taking Acomplia should consult their doctor or pharmacist at a convenient time to discuss their treatment.

- There is no need for patients to stop treatment with Acomplia immediately, but patients who wish to stop can do so at any time.

What is the advice to patients currently included in clinical trials with Acomplia?

As for all clinical trials, patients included in trials with Acomplia are closely monitored. Patients currently included in clinical trials with Acomplia should contact the investigator (the doctor who is giving them treatment). The investigator will be able to provide more information.

A European Commission decision on this opinion will be issued in due course.

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