Procedural steps taken and scientific information after the authorisation

Zimulti

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
EMEA/H/C/ 000691/A20/ 0012	Pursuant to Article 20 of Regulation (EC) No 726/2004 of 31 March 2004, the European Commission requested on 20 October 2008, the opinion of the CHMP on measures necessary to ensure the safe of further to an increased concern over psychiatric adverse events.	23/10/2008	Marketing Authorisation withdrawn on 16/01/2009 Please refer to Public Statement	Marketing Authorisation withdrawn on 16/01/2009 Please refer to Public Statement	Please refer to the Scientific Conclusions: EMEA/H/C/000691/A20/0012
II/0011	Update (based on the third PSUR) of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) to include a further warning related to depressive reactions and a new warning concerning diabetic patients as well as to add hypoglycaemia and tremor as uncommon adverse reactions and psychotic disorders (including hallucinations, delusion and paranoia), rash, convulsions, disturbance in attention, headache and abdominal pain as post-marketing adverse reactions. Relevant sections of the Package Leaflet (PL) were amended accordingly. An editorial correction was made in Annex II.	30/05/2008	17/07/2008	SPC, Annex II, PL	Following the third PSUR assessment, the CHMP concluded that depression may occur as a side effect of Zimulti in patients who have no obvious risk factors, apart from obesity itself. More than half of the patients who develop such side effects do so within one month of starting treatment, and approximately 80% do so within three months. Consequently, the CHMP recommended an update of the product information to reflect this new information and to advise prescribers to monitor patients for signs and symptoms of psychiatric disorders, particularly depression, after the start of treatment. Additionally, cumulative reviews were performed by the Marketing Authorisation Holder (MAH) for a number of adverse reactions such as hypoglycaemia, tremor, psychotic disorders, rash, convulsions, disturbance in attention, headache and abdominal pain. Further to these cumulative reviews, the CHMP recommended to include all these adverse reactions in section 4.8 of the SPC as well as to add a new warning in section 4.4 to inform prescribers that monitoring of blood glucose levels is recommended in diabetic patients.

[1] Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments
[2] SPC (Summary of Product Characteristics), Labelling, PL (Package Leaflet)

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II/0010	Changes in the manufacturing process of the active substance.	24/01/2008	29/01/2008		
II/0004	Update of Summary of Product Characteristics and Package Leaflet Update of section 5.1 of the Summary of Products Characteristics (SPC) to include data from two clinical trials performed in type 2 diabetic patients. Update of section 4.8 to include "paresthesia". Update of the relevant sections of the Package Leaflet in accordance to the SPC changes.	20/09/2007	23/10/2007	SPC, PL	Please refer to the scientific discussion Zimulti-H-C-691-II-04-AR
II/0008	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.3 of the Summary of Product Characteristics (SPC) to reflect a new contraindication in patients with ongoing major depression and/or ongoing antidepressive treatment. In addition, a warning including additional information on psychiatric safety has been included in section 4.4 of the SPC and section 4.8 has been updated with psychiatric adverse events (suicidal ideation, aggressiveness and aggressive behaviour). The Package Leaflet has been updated accordingly.	19/07/2007	31/08/2007	SPC, PL	On June 2006, the CHMP discussed the psychiatric safety of Zimulti and requested the MAH to provide all available data with regards to psychiatric events (mainly suicidal- and depression-related events) in patients treated with Zimulti. The CHMP also requested the MAH to propose a modification of the product information accordingly. These CHMP requests have been addressed through the present variation. The MAH provided all available data on psychiatric adverse events from spontaneous reporting and from clinical trials conducted after the granting of the Marketing Authorisation. Some of these clinical trials were still ongoing at the time of submission of the data. The provided data suggest that the risk of depression is approximately doubled in patients taking Acomplia, compared to obese or overweight patients not taking the medicine. In a small minority of cases, this could lead to suicidal ideation or even suicide attempts. This doubling of the risk of depression occurs in all types of patients; however, this risk may be increased in patients with a past history of depression. Although this pattern of side effects is similar to what was seen during the approval procedure of the medicine, the CHMP concluded that this increased risk of concern, since

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					Acomplia is now being used in patients with a history of psychiatric events. This could result in patients with depression being at risk of their disease getting worse. Additional exposure data show that too many patients are given rimonabant together with anti-depressant drug. Already in the present SPC there is a warning for this combination and in this variation it is agreed that this warning is strengthened to be a contraindication. The CHMP concluded that the benefits of Zimulti continue to outweigh its risk, except in patients with ongoing major depression or taking antidepressants. In addition, the CHMP recommended the addition in the product information of a stronger warning regarding psychiatric safety, including that treatment should be stopped if a patient develops depression. The product information was as well updated with psychiatric adverse events (suicidal ideation, aggressiveness and aggressive behaviour).

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IB/0009	17_a_Change in re-test period of the active substance		08/08/2007
IB/0007	42_a_01_Change in shelf-life of finished product - as packaged for sale	SPC	02/07/2007
IA/0006	41_a_01_Change in pack size - change in no. of units within range of appr. pack size	SPC, Labelling, PL	27/03/2007
IA/0005	41_a_01_Change in pack size - change in no. of units within range of appr. pack size	SPC, Labelling, PL	27/03/2007
IA/0003	11_a_Change in batch size of active substance or intermediate - up to 10-fold		14/09/2006
IB/0002	07_a_Replacement/add. of manufacturing site: Secondary packaging site 07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release 07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms 08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	SPC, Labelling, PL	16/08/2006
IA/0001	37_a_Change in the specification of the finished product - tightening of specification limits		03/08/2006

[3] Minor changes e.g. Type I variations and Notifications
[4] Date of entry into force of the change