London, 15 September 2005
Product name: Xeristar
Procedure number: EMEA/H/A-18/652

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.eu.int http://www.emea.eu.int

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION

Following a request from the European Commission, the CHMP reviewed the data from clinical trials available to the national competent authorities for the following SSRI[1]/SNRIs[2] products particularly as regards their use in the paediatric population: fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, atomoxetine, duloxetine, venlafaxine, mianserine, milnacipran, reboxetine, and mirtazapine.

The data reviewed included short-term placebo controlled randomised clinical trials submitted to the competent authorities, randomised clinical trials published in the medical literature, observational studies and ecological studies. The majority of trials included patients with major depressive disorders (MDD) while a few included patients with various anxiety disorders (Obsessive Compulsive Disorder (OCD), Generalised Anxiety Disorder (GAD), and Social Anxiety Disorder (SAD)). In addition there were some trials with patients suffering from Attention Deficit/Hyperactivity Disorder (ADHD).

These products are not authorised Europe-wide for the treatment of depression and anxiety disorders in children or adolescents. Only some of these products are authorised for the treatment of children and adolescents with obsessive-compulsive disorder and only one of them for the treatment of Attention Deficit/Hyperactivity Disorder.

Examination of suicide-related behaviours indicated that no completed suicide was reported in any of the reviewed studies. However, there was a clear suicide-related behaviours signal from the depression studies and a less strong signal from the anxiety studies. Moreover there was a signal concerning related adverse events like hostility, self-harm and emotional lability in almost all products and indications.

With the preliminary review of the data available to the national competent authorities the CHMP concluded that there were grounds for concerns about increased suicide-related behaviours in paediatric populations. The CHMP agreed that there was a potential signal of an increase in suicidal behaviour, including suicide attempts and suicidal ideation and/or related behaviour like self-harm, hostility and mood lability in children and adolescents treated with SSRIs and SNRIs. This signal was present in all products for which studies were available, and from the available evidence it could not be excluded that this signal would be class related.

Following the review of the data available to the national competent authorities, the European Commission triggered on 17 December 2004 a procedure under Article 18 of Council Regulation (EEC) No 2309/93 for medicinal products containing duloxetine. In parallel to this procedure, a referral procedure under article 31 of Directive 2001/83/EC, as amended, for medicinal products containing atomoxetine, citalopram, escitalopram, fluoxetine, fluvoxamine, mianserine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline and venlafaxine was triggered.

1 SSRI stands for 'Serotonin-Selective Reuptake Inhibitor'. SSRIs are described as 'selective' because they affect only the reuptake pumps responsible for serotonin.

2 SNRI stands for 'Serotonin-Norepinephrine Reuptake Inhibitor'. SNRIs work on the norepinephrine and serotonin neurotransmitters

The CHMP reviewed the data submitted by the MAHs in relation to the signal of suicidal behaviour in children and adolescents. The CHMP concluded that a warning to reflect that suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo, should be included in the Summary of Product Characteristics and relevant section of the Package Leaflet of Xeristar.

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

Whereas

- The Committee considered the procedure under Article 18 of Council Regulation (EEC) No 2309/93 for medicinal products containing duloxetine

- The Committee, in view of available data from clinical trials, concluded that there is a signal of suicidal behaviour, including suicide attempts and suicidal ideation and/or related behaviour like self-harm, hostility and mood lability in children and adolescents treated with Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors,

- The Committee, as a consequence, concluded that a warning to reflect that suicide-related behaviours (suicide attempt and suicidal thoughts), and hostility (predominantly aggression, oppositional behaviour and anger) were more frequently observed in clinical trials among children and adolescents treated with antidepressants compared to those treated with placebo, should be included in the Summary of Product Characteristics and relevant section of the Package Leaflet of Xeristar.

The CHMP has recommended the amendment to the terms of the Marketing Authorisation for Xeristar.

