Electronic Signature Page

Full Title
Lu 26-054 Escitalopram RMP Part 06 Summary of the risk management plan

Report Number/Short Title
Lu 26-054 Escitalopram RMP Part 06 Summary of the risk management plan

The following persons have electronically signed this document

Server Date and Time	Signed by
22-Feb-2013 15:37:46	EVAJ Eva Elstrup Jensen
Reason for Signature	Clinical Safety Approval

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Reason for Signature	

Risk Management Plan

Part VI – Summary of Activities in the Risk Management Plan by Product

Escitalopram

Brand name(s):	Cipralex, Entact, Esertia, Lexapro, Premalex, Prilect, Seroplex, Sipralexa
Data lock point:	31 December 2012
Date of report:	21 February 2013
Responsible person for Risk Management Plan:	Elin Heldbo Reines, MD, GPV Safety Operations & Surveillance
Qualified Person for Pharmacovigilance	Janne Malene Kampmann, M.Sc, GPV Safety Operations & Surveillance

Global Pharmacovigilance (GPV)
H. Lundbeck A/S
Ottiliavej 9 DK-2500
Copenhagen-Valby
Denmark
Telephone: (+45) 36 30 13 11
Fax: (+45) 36 30 99 67

Module version No.: 1

Table of Contents

Part VI Summary of activities in the risk management plan by product

Part VI.1 Elements for summary tables in the EPAR

Escitalopram is not a centrally authorised medicinal product.

Part VI.1.1 Summary table of safety concerns

Table 1 Summary of safety concerns

Important identified risks	Electrocardiogram QT prolonged
Important potential risks	Suicide related events Seizures Serotonin syndrome Diabetes Mellitus
Important missing information	Off label use (including off label use in paediatrics) Use during pregnancy and lactation

Part VI.1.2 Table of on-going and planned additional PhV studies / activities in the Pharmacovigilance Plan

There are no ongoing or planned pharmacovigilance studies or activities as all risks are well characterised and adequately monitored, why routine pharmacovigilance activities are considered sufficient.

Part VI.1.3 Summary of post-authorisation efficacy development plan

There is no post-authorisation efficacy development plan.

Part VI.1.4 Summary table of Risk Minimisation Measures

Table 2 Summary of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Electrocardiogram QT prolonged	Text in Core SmPC section 4.8, and 4.9.	None
Suicide related events	Text in Core SmPC sections 4.4, and 4.8	None
Seizures	Text in Core SmPC sections 4.4, 4.5, 4.6, 4.8 (as convulsion), and 4.9	None
Serotonin Syndrome	Text in Core SmPC sections 4.4, 4.5, 4.8, and 4.9	None
Diabetes Mellitus	Text in Core SmPC sections 4.4	None
Off label use in paediatrics	Text in Core SmPC sections 4.2, and 4.4	None
Use in Pregnancy and lactation	Text in Core SmPC sections 4.6	None

Part VI.2 Elements for a Public Summary

Part VI.2.1 Overview of disease epidemiology

Escitalopram is prescribed for the psychiatric disorders called mood disorders: major depressive disorder (MDD), obsessive compulsive disorders (OCD), panic disorder (with and without agoraphobia, PD), anxiety disorders and premenstrual dysphoric disorder (PMDD).

Up to 5% of the population report having been depressed in the previous year, and as many as 13% report being depressed in their lifetime. Depression is twice as frequent in women as in men. Its main danger lies in the risk of death by suicide associated with low mood and feeling of worthlessness which is 20 times more frequent in depressed individuals than in the general population. The incidence of type II diabetes and cardiovascular diseases is increased by 60% in depressed patients.

Approximately 20% of the population will at some point during their life experience an anxiety disorder. With the exception of obsessive compulsive disorders, women are at greater risk. While the major risk of OCD lies in suicide, major risks related to anxiety disorders are the confusion of somatic symptoms with somatic diseases. Depression and anxiety disorders are very often co morbid, and daily life and quality of life can be much impacted by these conditions.

Treatment options for these disorders include psychotherapy, antidepressants and anti-anxiety drugs.

PMDD is a severe form of pre-menstrual syndrome affecting from 3% to 5% of women of reproductive age. Mood symptoms can have an important impact on the daily life. Treatment options include antidepressants and oral contraception.

Part VI.2.2 Summary of treatment benefits

Escitalopram has in the clinical development program consistently proven to be efficacious and well tolerated in all the approved indications, and has also shown advantages in comparator trials in both efficacy and tolerability, versus both SSRIs and SNRIs.

MDD

MDD affects more than 16% of adults at some point during their lifetime. MDD is generally diagnosed when a persistent low mood and loss of all interest and pleasure are accompanied by a range of other specific symptoms, including appetite loss, insomnia, fatigue, loss of energy, poor concentration, psychomotor symptoms, inappropriate guilt and morbid thoughts of death.

Although pharmacological and psychological interventions are both effective for major depression, antidepressant drugs remain the mainstay of treatment. During the last 20 years, selective serotonin reuptake inhibitors (SSRIs) have progressively become the most commonly prescribed antidepressants.

Second-generation antidepressants dominate the medical management of depressive disorders. These drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and other drugs with related mechanisms of action that selectively target neurotransmitters.

Escitalopram is considered suitable as first-line antidepressant treatment for people with moderate to severe major depression.

In a large meta-analysis with 117 clinical trials with more than 25.000 subjects, escitalopram and sertraline showed the best profile of acceptability, leading to significantly fewer discontinuations than duloxetine, fluvoxamine, paroxetine, reboxetine, and venlafaxine. It showed that clinically important differences exist between commonly prescribed anti-depressants for both efficacy and acceptability in favour of escitalopram and sertraline.

Another review covers randomized, controlled studies in adult patients with MDD showed that escitalopram was superior to placebo, and equal or superior to other SSRIs (e.g. citalopram, paroxetine, fluoxetine, sertraline) and SNRIs (e.g., duloxetine, sustained-release venlafaxine). In addition, with long-term administration, escitalopram has shown a preventive effect on relapse and recurrence in remitted patients with MDD. Escitalopram also showed favorable tolerability and associated adverse events were generally mild and transient. Discontinuation symptoms were milder with escitalopram than with paroxetine.

Anxiety Disorders

Anxiety disorders are among the most prevalent of mental disorders (a life time prevalence of approximately 20%), and anxiety disorders share self-reported symptoms of anxiety and fear.

SSRIs are effective across the range of anxiety disorders and are generally suitable for first line treatment. Other treatments may include tricyclic antidepressants, and benzodiazepines.

Generalised Anxiety Disorder is a common, typically chronic disorder, for which a range of drugs and psychological treatment is available. Current treatment guidelines recommend first line treatment with a selective serotonin reuptake inhibitor (SSRI) or pregabalin. It is uncertain whether combining drug and psychological treatments (e.g. cognitive-behaviour treatment) is associated with greater overall efficacy than with either treatment, given alone. Cognitive-behaviour treatment may reduce relapse rates, so it is recommended especially in longer term treatment.

For Panic disorder a range of pharmacological psychological and combination interventions are effective. SSRIs and venlafaxine are currently considered as first-line agents for patients with panic disorder (PD). In addition psychological treatment is recommended in acute treatment and especially recommendation for longer term treatment.

Social Anxiety Disorder is often not recognized in primary medical care, where it may be misconstrued as shyness. In acute treatment SSRIs are first line treatment, as are some benzodiazepines, SNRIs, and anticonvulsants (pregabaline). In longer term treatment it is recommended to consider cognitive therapy in combination with drugs.

OCD

OCD has a life time prevalence of approximately 2%, and the disorder typically follows a chronic course, waxing and waning in severity. Switching between pharmacological or psychological treatments with proven efficacy may be helpful in some patients, as may increasing dosage, tolerability permitting.

Drugs recommended are first line SSRIs and clomipramine, as well as psychological (exposure therapy and cognitive behavioural therapy). In long term treatment SSRIs are recommended as first choice. Routinely combination of drugs and psychological approaches is not recommended for initial treatment.

PMDD

Premenstrual Dysphoric Disorder (PMDD) is a common cause of physical, behavioral, and also social dysfunction in women. Often the associated symptoms are evident as irritability, which is relieved by the onset of, or during, menstruation. PMDD can severely disrupt the lives of some women to the extent that they seek medical treatment. The precise cause is unknown. SSRIs have been shown effective in relieving severe premenstrual symptoms when compared with placebo. The most common adverse effects of SSRIs include nausea, insom-

nia, headache and decreased libido. All SSRIs (fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, and clomipramine) were effective in reducing premenstrual symptoms.

There are no post-authorisation data that impacts on efficacy, other than supporting the established efficacy and safety seen in the pivotal trials.

Part VI.2.3 Unknowns relating to treatment benefits

In the main and supporting studies nearly all patients were Caucasians, mean age was approximately 40 years, and approximately twice as many women were included compared to men. Studies have also been conducted in elderly patients aged at least 65 years, and in the paediatric population, however Lundbeck has not applied for indication for the paediatric population. In depression, efficacy has been established for the full range of moderate and severe depression.

There is no evidence to suggest that results would be any different in non-white patients or in younger patients, and there is no difference in efficacy between genders.

Part VI.2.4 Summary of safety concerns

Table 3 Important identified risks

Risk	What is known	Preventability
Electrocardiogram QT prolonged (Change in the heart's electrical activity on the ECG)	A change in the QT interval reflects a change in the heart's electrical activity on the electrocardiogram (ECG). The clinical studies have not shown that escitalopram causes any clinically relevant change the QTc interval in the approved doses. Some QTc prolongation has been seen in dose higher than recommended doses in a study in healthy persons. There is no evidence of heart arrhythmia in treatment with escitalopram.	To administer escitalopram in line with the recommended doses in the SmPC.

Table 4 Important potential risks

Risk	What is known
Seizures (fits)	Fits (seizures or convulsion) are the result of an abnormal electrical discharge in the brain This is considered as a class effect for antidepressants, where seizure threshold may be changed. Escitalopram should be stopped, if fits occurs, and avoided in patients with unstable epilepsy.
Suicide related events	This includes both thinking and behaviour about suicide. The risk of suicide in patients with mental disorders is higher than that for patients without co-existent mental disorders. As improvement may not occur during the first few weeks of treatment with an antidepressant as escitalopram, patients should be watched carefully until improvement occurs.
Serotonin syndrome	The syndrome is the consequence of excessive stimulation of the central nervous system and peripheral serotonin receptors. It may be produced by large doses or by combinations of drugs with serotonergic effect. In all cases the most important step is to remove the offending agent, this means that if escitalopram is used with other similar drugs, it should be considered stopped or dose lowered.
Diabetes Mellitus	Treatment of a depression with an antidepressant drug, such as escitalopram, may change glycemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.

Table 5 Important missing information

Risk	What is known

Off label use in children and young people	Escitalopram is not recommended for use in children and adolescents under 18 years of age, due to a lack efficacy and safety data.
Use during pregnancy and breast feeding	Animal studies show that escitalopram can be found in breast milk. There is no evidence to show, that this causes harm, but mothers should not breast feed when taking escitalopram. There is no evidence to suggest, that escitalopram causes harm to the baby, however we do not have sufficient data in pregnant women. Use during pregnancy should not be done unless clearly needed.

Part VI.2.5 Summary of additional risk minimisation measures by safety concern

Besides the routine risk minimisation measures in the Core SmPC, there are no additional risk minimisation measures.

Part VI.2.6 Planned post authorisation development plan

Escitalopram is in its late stage life cycle. There were no post authorisation studies required as condition for granting the marketing authorisation.

Table 6 List of studies in the post-authorisation development plan

Study / activity (including study number)	Objectives	Safety concerns / efficacy issue addressed	Status	Planned date for submission of (interim and) final reports
None				

Part VI.2.7 Summary of changes to the Risk Management Plan over time

Table 7 Major changes to the Risk Management Plan over time

Version	Date	Safety concerns	Comment
1	6-Dec-2006	One potential risk: off-label use in children with OCD. No important identified risks.	First RMP
2	24-Feb-2009	One potential risk: off-label use in children and adolescents. No important identified risks.	Updated, including class wording on suicide related events
3	22-Apr-2010	One potential risk for escitalopram: off-label use in children and adolescents. No important identified risks.	Updated, including class wording on PPHN, and bone fractures
4	22-Mar-2012	Important identified risk: Electrocardiogram QT prolonged. Important potential risks, including those classified as class effects, are: • Seizures • Diabetes • Serotonin syndrome • Suicide related events Important missing information includes: • Use during pregnancy and lactation • Off-label use	Updated to new EU RMP template, including SmPC updates after EU work sharing procedure