VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Patients with major depressive episodes (MDE)

Twelve-month occurence of major depressive disorder in the United States is approximately 7%, with marked differences by age group such that the occurence in 18- to 29-year-old individuals is threefold higher than in individuals age 60 years or older. Females experience 1.5- to 3-fold higher rates than males beginning in early adolescence. The average age of onset ascertained retrospectively was 25.7 in the high-income and 24.0 in low- to middle-income countries. Functional impairment was associated with recency of MDE. In high-income countries, younger age was associated with higher 12-month prevalence; by contrast, in several low- to middle-income countries, older age was associated with greater likelihood of MDE. MDE is a significant public-health concern across all regions of the world and is strongly linked to social conditions.

Patients with panic disorder with or without agoraphobia:

Panic disorder with agoraphobia is an anxiety disorder in which a person has attacks of intense fear and anxiety. There is also a fear of being in places where it is hard to escape, or where help

might not be available. Agoraphobia usually involves fear of crowds, bridges, or of being outside alone. Panic with agoraphobia may be a more severe variant of panic disorder. In the general population, the 12-month occurence estimate for panic disorder across the United States and several European countries is about 2%-3% in adults and adolescents. Females are more frequently affected than males, at a rate of approximately 2:1. The overall occurence of panic disorder is low before age 14 years (<0.4%). The rates of panic disorder show a gradual increase during adolescence, particularly in females, and possibly following the onset of puberty, and peak during adulthood. The prevalence rates decline in older individuals.

Patients with social anxiety disorder (SAD) (social phobia):

The 12-month occurence estimate of social anxiety disorder for the United States is approximately 7%. Lower 12-month prevalence estimates are seen in much of the world, clustering around 0.5%-2.0%; average occurence in Europe is 2.3%. The 12-month occurence rates in children and adolescents are comparable to those in adults. Occurence rates decrease with age. The 12-month occurence for older adults ranges from 2% to 5%. In general, higher rates of social anxiety disorder are found in females than in males in the general population, and the gender difference in occurence is more pronounced in adolescents and young adults. Gender rates are equivalent or slightly higher for males in clinical samples, and it is assumed that gender roles and social expectations play a significant role in explaining the heightened help-seeking behavior in male patients.

Patients with generalised anxiety disorder (GAD):

The 12-month occurence of generalized anxiety disorder is 0.9% among adolescents and 2.9% among adults in the general community of the United States. The 12-month prevalence for the disorder in other countries ranges from 0.4% to 3.6%. The lifetime morbid risk is 9.0%. Females are twice as likely as males to experience generalized anxiety disorder. The occurence of the diagnosis peaks in middle age and declines across the later years of life. Individuals of European descent tend to experience generalized anxiety disorder more frequently than do individuals of non-European descent (i.e., Asian, African, Native American and Pacific Islander). Furthermore, individuals from developed countries are more likely than individuals from nondeveloped countries to report that they have experienced symptoms that meet criteria for generalized anxiety disorder in their lifetime.

Patients with obsessive-compulsive disorder:

Surveys have revealed the startling fact that obsessive-compulsive disorder has a lifetime occurence rate as high as 2% to 3% and a 6-month occurence rate of 1.6%. Obsessive-compulsive disorder often begins at an early age with a third or more cases starting at puberty. It can also begin in childhood; cases in children as young as 3 or 4 years have been reported. Females are affected at a slightly higher rate than males in adulthood, although males are more commonly affected in childhood.

VI.2.2 Summary of treatment benefits

Accord Escitalopram is used to treat depression (major depressive episodes) and anxiety disorders (such as panic disorder with or without agoraphobia, social anxiety disorder, generalised anxiety disorder and obsessive-compulsive disorder).

Major depressive episodes

Escitalopram has been found to be effective in the acute treatment of major depressive episodes in three out of four 8-weeks duration studies. In a study, 274 patients who had responded during an initial 8-week treatment with escitalopram 10 or 20 mg/day were treated with escitalopram at the same dose, or to placebo, for up to 36 weeks. In this study, patients receiving continued escitalopram experienced a significantly longer time for recurrence of major depressive episodes over the subsequent 36 weeks compared to those receiving placebo.

Social anxiety disorder

Escitalopram was effective in both three short-term (12- week) studies and in a 6 months social anxiety disorder recurrence prevention study.

Generalised anxiety disorder

Escitalopram in doses of 10 and 20 mg/day was effective in all four placebo-compared studies. In collective data from three studies there were 47.5% of 421 escitalopram-treated patients responded to the treatment where as 28.9% of 419 placebo-treated patients responded to the treatment.

Maintenance of effectiveness of escitalopram 20 mg/day was demonstrated in a 24 to 76 week, in 373 patients who had responded during the initial 12 week study.

Obsessive-compulsive disorder

In a study, after 24 weeks, both 10 and 20 mg/day escitalopram were superior as compared to placebo. Prevention of disorder recurrence was demonstrated for 10 and 20 mg/day escitalopram in patients who responded to Escitalopram earlier.

However, these studies were conducted for the reference product (Cipralex, H. Lundbeck A/S, Denmark) and no studies to evaluate the expected benefit were performed for Accord escitalopram, considering its similarity to the reference product.

VI.2.3 Unknowns relating to treatment benefits

Not applicable

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Alteration of the heart rhythm seen on ECG (Electrocardiogram QT prolonged)	Some patients have reported (not known: frequency can not be estimated from the available data) alteration of the heart rhythm (called "prolongation of QT interval", seen on ECG, electrical activity of the heart).	Yes By preventing the administration of escitalopram to the patients: • Born with or may have had an episode of abnormal heart rhythm (seen at ECG). • taking medicines that can

Risk	What is known	Preventability
		change heart beat By contacting doctor immediately, in case patient experience a fast or irregular heartbeat, fainting, collapse or dizziness on standing up which may indicate abnormal functioning of the heart rate. By informing the doctor if the patient has coronary heart disease or suffer or have suffered from heart problems or have recently had a heart attack.
Sexual disturbances (Sexual dysfunction)	Sexual disturbances (delayed ejaculation, problems with erection, decreased sexual drive and women may experience difficulties achieving orgasm).	The side effects usually disappear after a few weeks of treatment. Please be aware that many of the effects may also be symptoms of your illness and therefore will improve when you start to get better. If you experience these adverse events you should contact your doctor or go to the hospital straight away. [6]
Bone fracture	An increased risk of bone fractures has	Patients are advised to contact

Risk	What is known	Preventability
	been observed in patients taking this type of medicines.	their doctor if they get these side effects during treatment.
Bleeding disorder	Bleeding disorders including skin and mucous bleeding (ecchymosis) and low level of blood platelets (thrombocytopenia).	Patients are advised to tell their doctor if they have any other condition or illness, as their doctor may need to take this into consideration. In particular, tell doctor if they have a tendency to easily develop bleedings or bruises. Patients are advised to contact their doctor if they get these side effects during treatment.

Important potential risks

Risk	What is known
Suicide related events	If patients are depressed and / or have anxiety disorders they can sometimes have thoughts of harming or killing them self. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer. Patients may be more likely to think like this: • If they have previously had thoughts about killing or harming them self. • If they are a young adult. Information from clinical

	trials has shown an increased risk of suicidal behaviour in adults aged less than 25 years with psychiatric conditions who were treated with an antidepressant.
A potentially life threatening drug reaction that causes the body to have too much serotonin, a chemical produced by nerve cells (Serotonin syndrome)	If you have a high fever, agitation, confusion, trembling and abrupt contractions of muscles these may be signs of a rare condition called serotonin syndrome. Patients are advised not to take escitalopram film-coated tablets if they take other medicines, which belongs to a group, called MAO inhibitors, including selegiline (used in the treatment of Parkinson's disease), moclobemide (used in the treatment of depression) and linezolid (an antibiotic).
Male fertility	Citalopram, a medicine like escitalopram, has been shown to reduce the quality of sperm in animal studies. Theoretically, this could affect fertility, but impact on human fertility has not been observed as yet.
A serious condition in babies making the baby breathe faster and appear bluish (Persistent pulmonary hypertension of the newborn)	Make sure midwife and/or doctor know patient is on Escitalopram. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Escitalopram may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.
Fits (Seizures)	Patients are advised to tell their doctor if they are taking Mefloquin (used to treat Malaria), bupropion (used to treat depression) and tramadol (used to treat severe pain) due to a

	possible risk of a lowered threshold for seizures. If patients have epilepsy. Treatment with Escitalopram film-coated tablets should be stopped if seizures occur or if there is an increase in the seizure frequency.
Diabetes mellitus	If the patient has diabetes, treatment with escitalopram film-coated tablets may alter glycaemic control. Insulin and / or oral hypoglycaemic dosage may need to be adjusted.

Missing information

Risk	**What is known**
Off label use	Escitalopram film-coated tablets should normally not be used for children and adolescents under 18 years. Also, one should know that patients under 18 have an increased risk of side effects such as suicide attempts, suicidal thoughts and hostility (predominately aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Escitalopram film-coated tablets for patients under 18 because he / she decide that this is in their best interest. If doctor has prescribed Escitalopram film-coated tablets for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any symptoms listed above develop or worsen when patients under 18 are taking Escitalopram film-coated tablets. Also, the long-term safety effects concerning growth, maturation and cognitive and behavioural development of Escitalopram film-coated tablets in this age group have not yet been demonstrated.
Use in pregnancy and	Inform doctor if you are pregnant or planning to become

Risk	What is known
lactation	pregnant. Do not take Escitalopram film-coated tablets if you are pregnant unless you and your doctor have discussed the risks and benefits involved. If you take Escitalopram film-coated tablets during the last 3 months of your pregnancy you should be aware that the following effects may be seen in your newborn baby: trouble with breathing, bluish skin, fits, body temperature changes, feeding difficulties, vomiting, low blood sugar, stiff or floppy muscles, vivid reflexes, tremor, jitteriness, irritability, lethargy, constant crying, sleepiness and sleeping difficulties. If your newborn baby has any of these symptoms, please contact your doctor immediately. Make sure your midwife and/or doctor know you are on Escitalopram film-coated tablets. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Escitalopram film-coated tablets may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately. If used during pregnancy Escitalopram film-coated tablets should never be stopped abruptly. Do not take Escitalopram film-coated tablets if you are breast-feeding unless you and your doctor have discussed the risks and benefits involved. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or

Risk	What is known
	pharmacist for advice before taking this medicine.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
4.0	04 November 2014	As per the post approval commitment, Safety concerns are updated as below: *Important Identified Risks:* Electrocardiogram QT prolonged Sexual dysfunction Bone fractures	Safety concerns updated to make them in line with the reference product Cipralex

		Bleeding disorders *Important Potential Risks:* Suicide related events Seizures Serotonin syndrome Diabetes Mellitus Male infertility Persistent pulmonary hypertension of the newborn *Missing information:* Off label use Use in pregnancy and lactation	
3.0	01 September 2014	Safety concerns are updated as below: *Important Identified Risks:* Electrocardiogram QT prolonged Sexual dysfunction Bone fractures Bleeding disorders *Important Potential Risks:* Suicide related events Seizures Serotonin syndrome	As per NL day 50 comments RMP safety concerns updated in line with the concerns listed for the innovator RMP.

		Diabetes Mellitus Male infertility Persistent pulmonary hypertension of the newborn Off label use	
2.0	20-Nov-2013	Following risks were added: *Important Identified Risks:* Suicidal ideation/ behaviour Sexual dysfunction Serotonin syndrome Bone fractures Bleeding disorders *Important Potential Risks:* Seizures Off-label use *Missing Information:* Use in pregnancy and lactation	The previous important potential risk "Bone fractures" was upgraded as Important Identified risk. Part VI.2: Elements for a public summary was rewritten in a lay and understandable language.