VI.2 Elements for a public summary

Incidence and prevalence of target indication	major depressive episodes Depressive disorders are characterized by sadness severe enough or persistent enough to interfere with function and often by decreased interest or pleasure in activities. Diagnosis is based on the history. Depressive disorders occur at any age but typically develop during the mid teens, 20s, or 30s. In primary care settings, as many as 30% of patients report depressive symptoms, but < 10% have major depression. The exact cause is unknown, but genetic and environmental factors contribute to the occurence. Women are at higher risk, but no theory explains why. Possible factors include greater exposure to or heightened response to daily stresses, higher levels of monoamine oxidase (the enzyme that degrades neurotransmitters considered important for mood), higher rates of thyroid dysfunction, and endocrine changes that occur with menstruation and at menopause. panic disorder A panic attack is the sudden onset of a discrete, brief period of intense discomfort, anxiety, or fear accompanied by somatic or cognitive symptoms. Panic disorder is the occurrence of repeated panic attacks typically accompanied by fears about future attacks or changes in behaviour to avoid situations that might predispose such attacks. Diagnosis is clinical. Panic attacks are common, affecting as many as 10% of the population in a single year. Most people recover without treatment; a few develop panic disorder. Panic disorder is uncommon, affecting 2 to 3% of the population in a 12-month period. Panic disorder usually begins in late adolescence or early adulthood and affects women 2 to 3 times more often than men. social anxiety disorder Social phobia (social anxiety disorder): Social phobia is the fear of and anxiety about being exposed to certain social or performance situations. These situations are avoided or endured with substantial anxiety. People with social phobia recognize that their fear is unreasonable and excessive. Social phobia affects about 9% of women and 7% of men during any 12-month period, but the lifetime prevalence may be at least 13%. Men are more likely than women to have the most severe form of social anxiety, avoidant personality disorder. Fear and anxiety in people with social phobia often centers on being embarrassed or humiliated if they fail to meet expectations. Often the concern is that their anxiety will be apparent through sweating, blushing, vomiting, or trembling or that the ability to keep a train of thought or find words to express themselves will

be lost. Usually, the same activity done alone causes no anxiety.

generalised anxiety disorder

Generalized anxiety disorder (GAD) is characterized by excessive, almost daily anxiety and worry for ≥ 6 months about many activities or events. The cause is unknown, although it commonly coexists in people who have alcohol abuse, major depression, or panic disorder. Diagnosis is based on history and physical examination. Treatment is psychotherapy, drug therapy, or both.
GAD is common, affecting about 3% of the population within a 1-year period. Women are twice as likely to be affected as men. The disorder often begins in childhood or adolescence but may begin at any age.
The course is usually fluctuating and chronic, with worsening during stress. Most people with GAD have one or more other comorbid psychiatric disorders, including major depression, specific phobia, social phobia, and panic disorder.

obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is characterized by anxiety-provoking ideas, images, or impulses (obsessions) and by urges (compulsions) to do something that will lessen the anxiety. The cause is unknown. Diagnosis is based on history.
OCD occurs about equally in men and women and affects about 2% of the population.
Typically, affected people feel compelled to perform repetitive, purposeful rituals to balance their obsessions. Most rituals, such as hand washing or checking locks, are observable, but some mental rituals, such as silent repetitive counting or statements muttered under the breath, are not.
At some point, people with OCD recognize that their obsessions do not reflect real risks and that the behaviours they perform to relieve their concern are unrealistic and excessive. Preservation of insight, although sometimes slight, differentiates OCD from psychotic disorders, in which contact with reality is lost.

VI.2.2 Summary of treatment benefits

With respect to antidepressant effects, the efficacy signal in placebo-controlled studies of major depressive disorder is strong. The relative efficacy of escitalopram is strongest in subanalyses of patients with more severe depressive symptoms. Usually 2-4 weeks are necessary to obtain antidepressant response. After the symptoms resolve, treatment for at least 6 months is required for consolidation of the response.
Escitalopram is also effective and generally well tolerated in the treatment of moderate to severe generalized anxiety disorder (GAD) or social anxiety disorder (SAD), panic disorder (with or without agoraphobia) as well as obsessive-compulsive disorder (OCD). In panic disorder maximum effectiveness is reached after about 3 months. In social anxiety disorder treatment usually 2-4 weeks are necessary to obtain symptom relief and therapy for 12 weeks is recommended. In generalized anxiety disorder long term treatment benefits and dose should be re-evaluated at regular intervals. Similarly, OCD is a chronic disease, patients should be

treated for a sufficient period to ensure that they are symptom free and treatment benefits and dose should be re-evaluated at regular intervals.
A favourable pharmacokinetic profile permits once-daily administration of the drug.
Available clinical data indicate that escitalopram is an effective first-line treatment option for the management of major depressive disorder (MDD), GAD, SAD, panic disorder and OCD.

VI.2.3 Unknowns relating to treatment benefits

The efficacy of escitalopram in social anxiety disorder has not been studied in elderly patients.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Thoughts of killing or harming oneself (Suicidal behaviour, suicide ideation)	In the early stages of recovery from depression (especially the first 2 weeks) suicidal ideation/behavior is more prominent, which is especially true in the younger (less than 25 years old) patient population.	Yes, by monitoring for early symptoms and by informing the physician, close friends and relatives. If you <u>have</u> thoughts of killing or harming yourself at any time, **inform your physician without delay or seek for medical care in the closest medical facility.** **You will perhaps consider useful to inform your close friends or relatives** that you suffer from depressions or anxious disorders and to ask them to read the present Package Leaflet. You could ask them to tell you, if they believe that your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.
Heart rhythm problems (QT prolongation, ventricular arrhythmia including torsade de pointes)	Escitalopram has been found to cause dose-dependent heart rhythm problems, predominantly in patients of female gender, with decreased levels of potassium in the blood (hypokalaemia) as a result of vomiting and/or diarrhea or usage of diuretics (water tablets), or with pre-existing heart rhythm problems (QT-prolongation) or other types of heart diseases as well as in patients taking some other medications concomitantly. Caution is advised in patients with significant slowing of the heart rhythm; or in patients with history of a recent heart attack or uncompensated heart failure.	Yes, by having the physician take a thorough patient history, checking for concomitant medications, doing blood-work, running an ECG.

A life-threatening syndrome that develops due to high levels of the chemical serotonin (Serotonin syndrome)	Serotonin syndrome occurs when you take medications that cause high levels of the chemical serotonin to accumulate in your body. Serotonin syndrome can occur when you increase the dose of such a drug or add a new drug to your regimen. Serotonin syndrome symptoms typically occur within several hours of taking a new drug or increasing the dose of a drug you're already taking. Signs and symptoms include: Agitation or restlessness, confusion, rapid heart rate and high blood pressure, dilated pupils, loss of muscle coordination or twitching muscles, heavy sweating, diarrhea, headache, shivering, goose bumps. Severe serotonin syndrome can be life-threatening. Signs and symptoms include: High fever, seizures, irregular heartbeat, unconsciousness.	Yes, by being aware of the risk of serotonin syndrome when taking certain medicines or increasing their dosages as well as by having the physician take a thorough patient history, checking for concomitant medications, and monitoring the patient especially after increase of drug dosages and/or after certain drugs have been added to the therapy.

Important potential risks:

Risk	**What is known (Including reason why it is considered a potential risk)**
Stopping of the heart (Cardiac arrest)	Severe rhythm abnoramlities/slowing of the heart that have been associated with escitalopram can cause the heart to stop.

Risk	**What is known (Including reason why it is considered a potential risk)**
Increaed pressure in the eye (Angle closure glaucoma)	Recent exposure to antidepressant drugs is associated with an increased risk of acute angle closure glaucoma.

Risk	**What is known (Including reason why it is considered a potential risk)**
Bone fractures occurring without high force impact or stress, but rather due to trivial injury as a result of weakened bones (Pathological bone fractures)	Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

Risk	What is known (Including reason why it is considered a potential risk)
Condition of newborns in which the blood pressure in the lungs (pulmonary artery system) is higher than normal (Persistent pulmonary hypertension in neonates)	Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

Risk	What is known (Including reason why it is considered a potential risk)
Inflammation of the liver (Hepatitis)	The frequency of hepatitis associated with escitalopram administration is not known.

Risk	What is known (Including reason why it is considered a potential risk)
Male infertility	Animal data have shown that a similar medication (i.e. citalopram) may affect sperm quality. Human case reports with some SSRIs (i.e. same class of medicines as escitalopram) have shown that an effect on sperm quality is reversible. Impact on human fertility has not been observed so far.

Risk	What is known (Including reason why it is considered a potential risk)
Involuntary muscle contractions/convulsions/fits (Seizures)	A seizure is an episode of abnormal electrical activity in the brain which causes a person's body to shake rapidly and uncontrollably. SSRIs, including escitalopram, should be avoided in patients with unstable epilepsy and patients with controlled epilepsy should be closely monitored as an increase in seizure frequency is possible.

Risk	What is known (Including reason why it is considered a potential risk)
Abnormally elevated or irritable mood (Mania)	Mania is a state of abnormally elevated or irritable mood, arousal, and/or energy levels. SSRIs, should be used with caution in patients with a history of mania/hypomania and should be discontinued in any patient entering a manic phase.

Risk	What is known (Including reason why it is considered a potential risk)
Bleeding, because of problems with the clotting of blood (Haemorrhage due to altered anticoagulant effects)	There have been reports of cutaneous bleeding abnormalities, such as ecchymoses and purpura, with SSRIs. Caution is advised in patients taking SSRIs, particularly in concomitant use with oral anticoagulants, with medicinal products known to affect platelet function

Risk	What is known (Including reason why it is considered a potential risk)
Low levels of sodium in the blood (Hyponatraemia)	Hyponatraemia has been reported rarely with the use of SSRIs, and generally resolves on discontinuation of therapy.

	The elderly, patients with cirrhosis, or patients using a combination with other medications which may cause hyponatraemia, are at increased risk.

Risk	**What is known (Including reason why it is considered a potential risk)**
Unvoluntary, purposeless movements (Akathisia/psychomotor restlessness)	The use of SSRIs/SNRIs has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Risk	**What is known (Including reason why it is considered a potential risk)**
An herb/plant (St.John's Wort)	Concomitant use of SSRIs and herbal remedies containing St. John´s Wort (*Hypericum perforatum*) may result in an increased incidence of adverse reactions.

Risk	**What is known (Including reason why it is considered a potential risk)**
Anxiety symptoms that are being caused by the medication used to treat anxiety (Paradoxical anxiety)	Some patients with panic disorder may experience increased anxiety symptoms at the beginning of treatment with antidepressants. This paradoxical reaction usually subsides within two weeks during continued treatment. A low starting dose is advised to reduce the likelihood of an anxiogenic effect.

Risk	**What is known (Including reason why it is considered a potential risk)**
Build-up of a waxy substance within the blood vessels supplying the heart with oxygen (Coronary heart disease)	Coronary heart disease (CHD) is a disease in which a waxy substance called plaque builds up inside the coronary arteries. These arteries supply oxygen-rich blood to your heart muscle. Due to limited clinical experience, caution is advised in patients with coronary heart disease.

Important missing information

Risk	**What is known**
Not applicable	Not applicable

VI.2.5 Summary of additional risk minimisation measures by safety concern
No additional risk minimisation measures are considered necessary.

VI.2.6 Planned post authorisation development plan (if applicable)
Not applicable. No postauthorisation studies are planned.