VI.2  Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Epidemiology of depression

Depression is estimated to affect 350 million people worldwide. The World Mental Health Survey conducted in 17 countries found that on average about 1 in 20 people reported having an episode of depression in the previous year\(^1\). Depressive disorders are the fourth highest cause of disability worldwide\(^2\). In people aged 18-44 years, depression is the leading cause of disability and premature death. Depression is predicted to be second leading cause of disability in people of all ages by 2020\(^2\). At its worst, depression can lead to suicide. Almost 1 million lives are lost yearly due to suicide which translates to 3,000 suicide deaths every day\(^1\).

Lifetime prevalence rates range from approximately 3% in Japan to 16.9% in the United States, with most countries falling somewhere between 8 to 12%\(^1\). In people seen in primary care settings, the prevalence is between 5 and 10%\(^2\). Women are affected twice as much as men. In patients with an affected first-degree relative, the lifetime risk increases to 1.5 to 3 times the average. First onset most frequently occurs in patients aged 12-24 years (1.4% to 9.1%) and in those older than 65 years (1.3-1.8%)\(^2\).

The lack of standard diagnostic screening criteria makes it difficult to compare depression rates cross-nationally\(^1\). In the first report on the epidemiology of depressive disorders from the European Outcome of Depression International Network Study (ODIN) study, five centres were examined: Liverpool (UK), Dublin (Ireland), Oslo (Norway), Turku (Finland) and Santander (Spain). Each centre identified one rural and one urban setting in which to conduct its research. A wide difference in prevalence of depressive disorders across the study sites and between urban and rural centres was found. The centres fell into three categories: high prevalence (urban Ireland urban UK: 12.8-17.1% respectively), low prevalence (urban Spain: 2.6%) and medium prevalence (the rest of the sites: 6-9.3%). The prevalence of depressive disorders among responders in the four rural communities was relatively uniform, ranging between 6.5 and 9.3%. These differences in prevalence figures suggest that there are cultural differences or different risk-factor profiles between countries and sites which may affect the expression of the disorder\(^3\).

Bromet et al. presented data on prevalence of depression from 18 high- and low- to middle-income countries in the World Mental Health Survey Initiative\(^4\). Data were included from 10 high-income countries (Belgium, France, Germany, Israel, Italy, Japan, Netherlands, New Zealand, Spain, US) and 8 low-to middle-income countries (Brazil, Columbia, India, China,
Lebanon, Mexico, South Africa, Ukraine). The average lifetime and 12-month prevalence estimates of major depressive episodes were 14.6% and 5.5% in the ten high-income and 11.1% and 5.9% in the eight low- to middle-income countries. The authors did not specifically investigate why these differences exist. Differences in stress exposure, reactive stress and in endogenous depression unrelated to environmental provoking factors are all possibilities. It has been suggested that depression is an illness of affluence to some extent[4].

There is also evidence arising from the present economic crisis associating such economic crises with depression and suicide. A telephone survey carried out in Greece revealed a 36% increase in the reported number of suicides between 2009 and 2011[1].

Epidemiology of panic disorder with or without agoraphobia

A comprehensive literature search focusing on epidemiological studies in community and clinical settings in European countries since 1980 was conducted (Medline, Web of Science, Psychinfo). Only studies using established diagnostic instruments on the basis of DSM-III-R or DSM-IV, or ICD-10 were considered. Thirteen studies from a total of 14 countries were identified. Epidemiological findings are relatively consistent across the EU. The 12-month prevalence of panic disorder and agoraphobia without history of panic were estimated to be 1.8% (0.7-2.2) and 1.3% (0.7-2.0) respectively across studies. Rates are twice as high in females and age of first onset for both disorders is in adolescence or early adulthood. In addition to comorbidity with agoraphobia, panic disorder is strongly associated with other anxiety disorders, and a wide range of somatoform, affective and substance use disorders. Even subclinical forms of panic disorder (i.e., panic attacks) are associated with substantial distress, psychiatric comorbidity and functional impairment. In general health primary care settings, there appears to be substantial underdiagnosis and undertreatment of panic disorder. Moreover, panic disorder and agoraphobia are poorly recognized and rarely treated in mental health settings, despite high health care utilization rates and substantial long-term disability[10].

Epidemiology of social anxiety disorder

The prevalence of 12-month and lifetime DSM-IV SAD was 2.8% (95% CI = 2.5 to 3.1) and 5.0% (95% CI = 4.6 to 5.4), respectively has been evaluated. Being Native American, being young, or having low income increased risk, while being male, being of Asian, Hispanic, or black race/ethnicity, or living in urban or more populated regions reduced risk. Mean age at onset of SAD was 15.1 years, with a mean duration of 16.3 years. Over 80% of individuals with SAD received no treatment, and the mean age at first treatment was 27.2 years. Current and lifetime SAD were significantly related to other specific psychiatric disorders, most notably generalized anxiety, bipolar I, and avoidant and dependent personality disorders. The mean number of feared social situations among individuals with SAD was 7.0, with the majority reporting anxiety in performance situations.[11]

Epidemiology of generalised anxiety disorder

MEDLINE searches were performed and supplemented by consultations with experts across Europe to identify non-published reports. Despite variations in the design of studies,
available data suggest that (a) about 2% of the adult population in the community is affected (12-month prevalence), (b) GAD is one of the most frequent (up to 10%) of all mental disorders seen in primary care, (c) GAD is a highly impairing condition often comorbid with other mental disorders, (d) GAD patients are high utilizers of healthcare resources, and (e) despite the high prevalence of GAD in primary care, its recognition in general practice is relatively low. Marked data deficits are: lack of data from eastern European countries, lack of information about the natural course of GAD in unselected samples, the vulnerability and risk factors involved in the aetiology of GAD and lack of data about adequate and inappropriate treatments in GAD patients as well as the associated and societal costs of GAD.\(^{(12)}\)

**Epidemiology of obsessive-compulsive disorder**

Analyzed data on lifetime and annual prevalence rates, age at onset, symptom profiles, and comorbidity of obsessive compulsive disorder (OCD) from community surveys in 7 countries: the US, Canada, Puerto Rico, Germany, Taiwan, Korea, and New Zealand showed that the OCD annual prevalence rates were remarkably consistent among these countries, ranging from 1.1/100 in Korea and New Zealand to 1.8/100 in Puerto Rico. The only exception is Taiwan (0.4/100), which has the lowest prevalence rates for all psychiatric disorders. The data for age at onset, which ranged from 21.9 to 35.5 yrs, and comorbidity with major depression and the other anxiety disorders were also consistent among countries, but the predominance of obsessions or compulsions varied. Findings support the robustness of OCD as a disorder in diverse parts of the world, but the variability in symptom presentations suggests that cultural factors may affect the symptom expression.\(^{(13)}\)

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**VI.2.2 Summary of treatment benefits**

**Escitalopram: a review of its use in the management of major depressive disorder** \(^{(5)}\).

Escitalopram possesses a rapid onset of antidepressant activity, and is an effective and generally well tolerated treatment for moderate-to-severe major depressive disorder (MDD). Pooled analyses from an extensive clinical trial database suggest that escitalopram is consistently more effective than citalopram in moderate-to-severe MDD. Preliminary studies suggest that escitalopram is as effective as other SSRIs and the extended-release (XR) formulation of the serotonin/noradrenaline (norepinephrine) reuptake inhibitor venlafaxine, and may have cost-effectiveness and cost-utility advantages.

**Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebocontrolled trial** \(^{(6)}\).

Escitalopram, the therapeutically active isomer of the racemic selective serotonin reuptake inhibitor antidepressant citalopram, has shown significant anxiolytic effects in placebo-controlled clinical trials of social anxiety disorder, generalised anxiety disorder, and anxiety symptoms associated with major depression. This study evaluated the safety and efficacy of
escitalopram in outpatients diagnosed with panic disorder. Male and female outpatients between 18 and 80 years of age meeting DSM-IV criteria for panic disorder, with or without agoraphobia, were randomly assigned to 10 weeks of double-blind treatment with escitalopram, citalopram, or placebo in a study conducted from September 1999 to July 2001. The primary measure of efficacy was panic attack frequency at week 10 relative to baseline, as assessed by the Modified Sheehan Panic and Anticipatory Anxiety Scale. A total of 366 subjects (128 escitalopram patients, 119 citalopram patients, and 119 placebo patients) received at least 1 dose of double-blind treatment. The frequency of panic attacks was statistically significantly improved (p = .04), and the increase in percentage of patients with zero panic attacks reached borderline significance (p = .051), in the escitalopram-treated group relative to the placebo-treated group. Both escitalopram and citalopram statistically significantly reduced panic disorder symptoms and severity versus placebo at endpoint (p < .05), as measured by the Panic and Agoraphobia Scale total score, the Clinical Global Impressions scale, the Patient Global Evaluation, and the Quality of Life Enjoyment and Satisfaction Questionnaire. Treatment with escitalopram was safe and well tolerated, with a similar incidence of the most common adverse events for the escitalopram and placebo groups. The rate of discontinuation for adverse events was 6.3% for escitalopram, 8.4% for citalopram, and 7.6% for placebo. The authors concluded that escitalopram is efficacious and well tolerated in the treatment of panic disorder.

Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study [7].

Selective serotonin reuptake inhibitors are the pharmacological treatment of choice for the treatment of social anxiety disorder (SAD). The efficacy and tolerability of fixed doses of escitalopram were compared with those of placebo in the long-term treatment of generalised SAD, using paroxetine as an active reference. Patients with a DSM-IV diagnosis of SAD between 18-65 years of age were randomised to 24 weeks of double-blind treatment with placebo (n = 166), 5 mg escitalopram (n = 167), 10 mg escitalopram (n = 167), 20 mg escitalopram (n = 170), or 20 mg paroxetine (n = 169). Based on the primary efficacy parameter, Liebowitz Social Anxiety Scale (LSAS) total score at Week 12 (LOCF), a significantly superior therapeutic effect compared to placebo was seen for 5 and 20 mg escitalopram and for all doses for the OC analyses. Further improvement in LSAS scores was seen at Week 24 (OC and LOCF), with significant superiority over placebo for all doses of escitalopram. Response to treatment (assessed by a Clinical Global Impression-Improvement score < or = 2) was significantly higher for all active treatments than for placebo at Week 12. Clinical relevance was supported by a significant decrease in all the Sheehan disability scores, and the good tolerability of escitalopram treatment. It was concluded that doses of 5-20 mg escitalopram are effective and well tolerated in the short- and long-term treatment of generalised SAD.

Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study [8].

Escitalopram has been shown in clinical trials to improve anxiety symptoms associated with depression, panic disorder, and social anxiety disorder. This study was designed to evaluate the efficacy and tolerability of escitalopram in the treatment of generalised anxiety disorder (GAD). Outpatients (18 years or older) who met DSM-IV criteria for GAD, with baseline Hamilton Rating Scale for Anxiety (HAMA) scores > or = 18, were randomly assigned to double blind treatment with escitalopram (10 mg/day for the first 4 weeks and then flexibly dosed from 10-20 mg/day) or placebo for 8 weeks, following a 1-week, single-blind, placebo
The primary efficacy variable was the mean change from baseline in total HAMA score at Week 8. The escitalopram group (N = 158) showed a statistically significant, and clinically relevant, greater improvement at endpoint compared with placebo (N = 157) in all prospectively defined efficacy parameters. Significant improvement in HAMA total score and HAMA psychic anxiety subscale score for the escitalopram-treated group vs. the placebo-treated group was observed beginning at Week 1 and at each study visit thereafter. Mean changes from baseline to Week 8 on the HAMA total score using a last-observation-carried-forward (LOCF) approach were -11.3 for escitalopram and -7.4 for placebo (P<.001). Response rates at Week 8 were 68% for escitalopram and 41% for placebo (P<.01) for completers, and 58% for escitalopram and 38% for placebo LOCF values (P<.01). Treatment with escitalopram was well tolerated, with low rates of reported adverse events and an incidence of discontinuation due to adverse events not statistically different from placebo (8.9% vs. 5.1%; P=.27). The authors concluded that escitalopram 10-20 mg/day is effective, safe, and well tolerated in the treatment of patients with GAD.

Escitalopram: a review of its use in the management of anxiety disorders. Escitalopram is a potent and highly selective serotonin reuptake inhibitor. It is effective and generally well tolerated in the treatment of moderate to severe generalised anxiety disorder (GAD) or social anxiety disorder (SAD), panic disorder (with or without agoraphobia) as well as obsessive-compulsive disorder (OCD). Moreover, escitalopram is at least as effective as paroxetine for the treatment of GAD, SAD or OCD and appears to achieve a more rapid response than racemic citalopram in the management of panic disorder. Generally, it has a more favourable tolerability profile than paroxetine in terms of fewer discontinuation symptoms. A favourable pharmacokinetic profile permits once-daily administration of the drug.

VI.2.3 Unknowns relating to treatment benefits

There are limited data on the efficacy and safety of escitalopram during pregnancy.

VI.2.4 Summary of safety concerns

Important Identified Risks

<table>
<thead>
<tr>
<th>Risks</th>
<th>What is known</th>
<th>Preventability</th>
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<tbody>
<tr>
<td>Serotonin syndrome</td>
<td>Serotonin syndrome is a potentially life threatening drug reaction that causes the body to have too much serotonin, a chemical produced by nerve cells. Serotonin syndrome most often occurs when two</td>
<td>The prescribing physician should ask questions about patients’ medical history, including the types of drugs taken and advise patient to contact medical professional in case of experiencing symptoms such as high fever, agitation, confusion, trembling and abrupt contractions of muscles whilst being treated with escitalopram.</td>
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drugs that affect the body's level of serotonin are taken together at the same time. The drugs cause too much serotonin to be released or to remain in the brain area.

This syndrome can develop if patients take migraine medicines called triptans together with antidepressants called selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SSNRIs).

Serotonin syndrome is more likely to occur when patients first start or increase the medicine.

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<thead>
<tr>
<th>QT interval prolongation</th>
<th>Some patients have reported alteration of the heart rhythm (called “prolongation of QT interval”)</th>
<th>The prescribing physician should ask questions about patients’ medical history, including the types of drugs taken and advise patient to contact medical professional in case of experiencing alteration of the heart rhythm whilst being treated with escitalopram and to perform and ECG in order to diagnose the event.</th>
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<tr>
<td>Suicidal ideation, suicidal behaviour</td>
<td>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.</td>
<td>Prescribing physician should inform the patient and carer about this risk and advise them to medical professional or go to a hospital straight away if have thoughts of harming or killing themselves at any time. The patient taking escitalopram may find it helpful to tell a relative or close friend that they are depressed or have an anxiety disorder, and ask them to read the escitalopram leaflet and also to tell the patient/carer if they think the depression or anxiety is getting worse, or if they are worried about changes in patients’ behaviour.</td>
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<tr>
<td>Seizures</td>
<td>The use of escitalopram</td>
<td>The treating doctor should closely</td>
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<td>Loss of glycaemic control in diabetics</td>
<td>Treatment with escitalopram is know to alter glycaemic control (control of blood sugar levels) in diabetics</td>
<td>The treating physician may need to adjust the patients insulin and/or oral dosages in order to control their blood sugar levels. Patients must inform their treating doctor or pharmacist they have diabetes before taking escitalopram.</td>
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| Hyponatraemia | | |

### Important Potential Risks

<table>
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<th>Risks</th>
<th>What is known</th>
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<tr>
<td>Haemorrhage in patients co-administrated anti-coagulants or NSAIDs or other medicines increasing the risk of haemorrhage</td>
<td>The use of escitalopram has been associated with the risk of bleeding, particularly in concomitant use with anticoagulants (medicines used to thin the blood) or acetylsalicylic acid (aspirin) (used for pain relief or to thin the blood) and non-steroidal anti-inflammatory drugs (NSAIDs) (medicines used for pain relief).</td>
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### Important missing information

<table>
<thead>
<tr>
<th>Risks</th>
<th>What is known</th>
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<tr>
<td>Use in pregnancy and lactation</td>
<td>For escitalopram only limited clinical data are available regarding exposed pregnancies and breast feeding. In reproductive toxicity studies performed in rats with escitalopram, embryo-fetotoxic effects, but no increased incidence of malformations, were observed. The risk for humans is unknown. Therefore, Escitalopram tablets should not be used during pregnancy unless clearly necessary and only after careful consideration of the risk/benefit.</td>
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Neonates should be observed if maternal use of escitalopram continues into the later stages of pregnancy, particularly in the third trimester. Abrupt discontinuation should be avoided during pregnancy.

Off-label use

The prescribing physician must be aware of the risk of prescribing off-label escitalopram.

Patients instructed to read section 2 and 3 of the PIL for information on the proper use of the medicinal product.

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

No additional risk minimisation measure has been suggested for escitalopram. Routine risk minimisation measure includes addition of information in various safety sections of the SPC and PIL to make healthcare professional and patient aware about the safety concerns.

VI.2.6. Planned post authorisation development

No post authorisation development has been planned or been performed.

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

This is the initial RMP (Version 1) prepared for the generic application of Escitalopram 5, 10, 15 & 20 mg film-coated tablets by Mylan AB.