VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Paroxetine is used to treat conditions such as major depressive episode, Obsessive Compulsive Disorder (OCD), panic disorder with and without agoraphobia, social anxiety disorders/social phobia, generalised anxiety disorder and post-traumatic stress disorder.

Two recent epidemiologic studies suggest that Major Depressive Episode (MDD) is very common and also occurs with high rates of comorbidity(complicated by the presence of other psychiatric disorders) The national comorbidity survey reported a lifetime prevalence of MDD of 12.7% in male patients,21.3% in female patients, and overall,17.1%.The national comorbidity survey replication study showed similar data. Thus MDD is a common condition and occurs in women more frequently than in men. In contrast, bipolar mood disorders are estimated to have a lifetime prevalence of 6 to 8% including the "bipolar spectrum" disorders.MDD occurs in all cultures and affects all age groups childhood and the adult onsets are common, and the mean age of onset is generally in the 30s.[1]

Obsessive–Compulsive Disorder (OCD) is the fourth most common mental disorder afterdepression, alcohol and substance misuse, and social phobia with a lifetimeprevalence in community surveys of about 2–3% (Robins et al., 1984). Howeverthe instruments used have been criticised and may have over-diagnosed OCD sothat the true prevalence may be somewhat lower (Stein et al., 1997b). Thereis remarkable consistency in the lifetime and annual prevalence of OCD fromstudies conducted across the world (Weissman et al., 1994). The mean age of onsetis in late adolescence for men and early twenties for women, although age ofonset covers a wide range of ages. However, it may take individuals between 10–15years or longer to seek professional help. There is often combordity with a rangeof disorders, especially depression[2].In a 2001 World Health Organization mental health report, it was estimated that, in the year 2000, OCD was among the top 20 causes of illness-related disability,

[1]DavidL.Dunner, MD, from S.H.fatemi and P.J. Clayton (eds.): The medical Casis of Psychiatry 2008 Humana Press, Tolowa,NJ.

[2] Core interventions in thetreatment of obsessivecompulsivedisorderand body dysmorphicdisorder.publishedbyThe British Psychological Society andThe Royal College of Psychiatrists.

worldwide, for individuals between 15 and 44 years of age. Moreover, many other research reports cite OCD as the fourth most common mental illness after phobias, substance abuse, and major depression.In the past, OCD was thought to be rare in children and adolescents. Studies conducted over the past several years, however, have shown that the lifetime prevalence of OCD in young people, worldwide, is approximately 1-2% (lifetime prevalence of OCD refers to the percentage of individuals in a given statistical population who, at some point in their lives, have experienced a case of OCD). Research also suggests that the prevalence rate for OCD is lower among young children and increases during childhood and adolescence. Another figure commonly referred to in the OCD research is that at any one given point in time, OCD affects approximately 1 in 100 children. Overall, OCD has been found to be one of the most common psychiatric illnesses affecting children and adolescents. Therefore, it is probable that the large majority of school personnel have encountered and/or will encounter students with OCD during their professional careers.OCD doesn't discriminate. It affects children and adults of both genders, all races and ethnicities. It occurs in every socioeconomic level and all over the U.S. and the world. Moreover, prevalence rates of OCD appear to be very similar worldwide. In clinical samples, however, OCD is found more often among Caucasian than minorities. This may be due to the underrepresentation of minorities in clinical studies.[3]

A comprehensive literature search focusing on epidemiological studies incommunity and clinical settings in European countries since 1980 was conducted (Medline, Web of Science, Psychinfo). Only studies usingestablished diagnostic instruments on the basis of DSM-III-R or DSM-IV, or ICD-10 were considered. Thirteen studies from a total of 14countries were identified. Epidemiological findings are relatively consistent across the EU. The 12-month prevalence of panic disorder andagoraphobia 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 ashigh 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 functionalimpairment. 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 careutilization rates and substantial long-term disability[4].

Epidemiologic surveys conducted across Europe indicate that the lifetime prevalence of social anxietydisorder in the general population is close to 7%. The disorder in adulthood rarely presents in its 'pure' formand 70–80%of patients have at least one other psychiatric disorder, most commonly depression. Social anxiety disorder is a riskfactor for the development of depression and alcohol/substance use or dependence, especially in cases with an earlyonset (< 15 years). Individuals with social anxiety disorder have significant functional impairment, notably in the areasof initiation and maintenance of social/romantic relationships and educational and work achievement. The economicconsequences of social anxiety disorder are considerable, with a high level of diminished work productivity, unemploy-ment and an increased utilisation of medical

[3]http://www.ocdeducationstation.org/ocd-facts/incidence-of-ocd/
[4]R.D. Goodwina,, C. Faravellib, S. Rosib, F. Coscib, E. Trugliab, R. de Graaf c, H.U. Wittchen,The epidemiology of panic disorder and agoraphobia in Europe:EuropeanNeuropsychopharmacology 15 (2005) 435 – 443

services amongst sufferers. Effective treatment of social anxiety disorderwould improve its course and its health and economic consequences[5].

Generalized anxiety disorder epidemiologicdatasuggest that (a) about 2% of the adult population in thecommunity 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 healthcareresources, and (e) despite the high prevalence of GAD in primary care, its recognition in general practice is relatively low. Marked datadeficits are: lack of data from eastern European countries, lack of information about the natural course of GAD in unselected samples, thevulnerability and risk factors involved in the aetiology of GAD and lack of data about adequate and inappropriate treatments in GAD patientsas well as the associated and societal costs of GAD[6].

Lifetime prevalence of exposure to potentially traumatic experiences (PTEs) varies considerably between countries and, within countries, between certain groups. Reported prevalence rates are 21.4% in Germany, 63.6% in a sample from 6 European countries, 64.6% of males and 49.5% of females in Australia, and 80.7% in the Netherlands. Higher rates of exposure have been reported in inner cities and where natural disasters have occurred. Certain groups are more likely to be exposed to PTEs: these include military personnel, emergency-service workers, police, and refugees. Estimates of lifetime prevalence of PTSD also vary between countries, with reports of 6.8% in the US, 1.3% in Germany, 1.9% across 6 European countries, and 7.4% in the Netherlands. The range of 12-month prevalence estimates reported is smaller: 3.6% in the US, 0.6% in South Africa, 0.7% in Germany, 1.1% across 6 European countries, and 1.3% in Australia. In the UK, although exposure to PTEs since the age of 16 has been reported as only 33% in adults, current PTSD was reported as 3%[7]..

VI.2.2 Summary of treatment benefits

Paroxetine is a selective Serotonin Re-uptake Inhibitor (an SSRI) medicine. It affects the transmission of chemical messages in the brain and nervous system. And is used to treat conditions such as depression, obsessive compulsive disorder, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalised anxiety disorder and post-traumatic stress disorder.

No additional studies were conducted as paroxetineAurobindois a generic medicine that is given by oral and contains the same active substance as the reference medicine, Seroxat®.

Because paroxetineAurobindois a generic, its beneficial treatment effects are taken as being the same as the reference medicine's.

VI.2.3 Unknowns relating to treatment benefits

[5]Y. Lecrubier , H.U. Wittchen , C. Faravelli , J. Bobes , A. Patel , M. Knapp:A European perspective on social anxiety disorder:Eur Psychiatry 2000 ; 15 : 5–16.

[6]RoselindLieb, Eni Becker, Carlo Altamura.,The epidemiology of generalized anxiety disorder in Europe;EuropeanNeuropsychopharmacology 15 (2005) 445 – 452.

[7]http://bestpractice.bmj.com/best-practice/monograph/430/basics/epidemiology.html

There is no information onuse of paroxetine in children less than 7 years. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking [eMCSmPC (2012)].

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Akathisia	Akathisia, or acathisia, is a syndrome characterized by unpleasant sensations of inner restlessness that manifests itself with an inability to sit still or remain motionless. The frequency is *rare*for persons being treated with Paroxetine.	Physician supervision and care.
Convulsions	A convulsion is a medical condition where body muscles contract and relax rapidly and repeatedly, resulting in an uncontrolled shaking of the body. The frequency is *rare*for persons being treated with Paroxetine.	Physician supervision and care.
Drug-drug interaction with MAOIs, Thioridazine, and Pimozide	Paroxetine is contraindicated in combination with monoamine oxidase inhibitors (MAOIs).	Physician supervision and Care.
Glaucoma	Glaucoma is a term describing a group of ocular disorders with multi-factorial etiology united by a clinically characteristic intraocular pressure-associated optic neuropathy. This can permanently damage vision in the affected eye(s) and lead to blindness if left untreated. The frequency is *Very rare* for persons being treated with paroxetine.	Physician supervision and Care.
Haemorrhage	Bleeding, technically known as hemorrhaging or hæmorrha ging is the loss of blood or blood escaping from the circulatory system. The frequency is *Very rare* for	Physician supervision and Care.

Risk	What is known	Preventability
	persons being treated with paroxetine.	
Hepatic events	Hepatic events (such as hepatitis, sometimes associated with jaundice and/or liver failure). The frequency is *Very rare*for persons being treated with paroxetine.	Physician supervision and Care.
Hyponatraemia	Hyponatraemia is an electrolyte disturbance in which the sodium ion concentration in the serum is lower than normal. Sodium is the dominant extracellular cation (positive ion) and cannot freely cross from the interstitial space through the cell membrane, into the cell	Physician supervision and Care.
Mania/Hypomania	Mania is a state of abnormally elevated or irritable mood, arousal, and/or energy levels. In a sense, it is the opposite of depression. Mania is a necessary symptom for certain psychiatric diagnoses.	Physician supervision and Care.
Serotonin Syndrome/ Neuroleptic Malignant Syndrome Like Events	Serotonin syndrome is a potentially life-threatening drug reaction that may occur following therapeutic drug use, inadvertent interactions between drugs, overdose of particular drugs, or the recreational use of certain drugs. The frequency is *Very rare*for patients being treted for Paroxetine.	Physician supervision and Care.
Suicidality (Suicidal ideation and suicidal behavior)	Suicidal ideation is a medical term for thoughts about or an unusual preoccupation with suicide. The range of suicidal ideation varies greatly from fleeting to detailed planning, role playing, self-harm and unsuccessful attempts, which may	Physician supervision and Care.

Risk	What is known	Preventability
	be deliberately constructed to fail or be discovered, or may be fully intended to result in death. The frequency is not known for suicidal ideation and suicidal behaviour	
Withdrawal Syndrome	Withdrawal is the group of symptoms that occur upon the abrupt discontinuation or decrease in intake of medications or recreational drugs.	Physician supervision and Care.

Important potential risks

Risk	What is known	Preventability
Congenital Disorders	A congenital disorder, is a condition existing at birth and often before birth, or that develops during the first month of life (neonatal disease), regardless of causation	Physician supervision and Care.

Missing information

Risk	What is known
Use in children under 7 years of age	The use of paroxetine has not been studied in children less than 7 years. Paroxetine should not be used, as long as safety and efficacy in this age group have not been established.
Long-term safety data in children and adolescents	***Children and adolescents (7-17 years)*** Paroxetine should not be used for the treatment of children and adolescents as controlled clinical trials have found paroxetine to be associated with increased risk for suicidal behaviour and hostility. In addition, in these trials efficacy has not been adequately demonstrated. ***Children aged below 7 years*** The use of paroxetine has not been studied in children less than 7 years. Paroxetine should not be used, as long as safety and efficacy in this age group have not been established.

Use in children and adolescents under 18 years of age

Paroxetine Aurobindo should not be used in the treatment of children and adolescents under the age of 18 years. 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. If, based on clinical need, a decision to treat is nevertheless taken; the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Adverse events from paediatric clinical trials

The following adverse events were observed:

Increased suicidal related behaviours (including suicide attempts and suicidal thoughts), self-harm behaviours and increased hostility. Suicidal thoughts and suicide attempts were mainly observed in clinical trials of adolescents with Major Depressive Disorder. Increased hostility occurred particularly in children with obsessive compulsive disorder, and especially in younger children less than 12 years of age.

Additional events that were seen are: decreased appetite, tremor, sweating, hyperkinesia, agitation, emotional lability (including crying and mood fluctuations), bleeding related adverse events, predominantly of the skin and mucous membranes.Events seen after discontinuation/tapering of paroxetine are: emotional lability (including crying, mood fluctuations, self-harm, suicidal thoughts and attempted suicide), nervousness, dizziness, nausea and abdominal pain (see section 4.4 Special Warnings and Special Precautions for use).

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

Not applicable

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

None.

Studies which are a condition of the marketing authorisation

None.

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

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Version 2.0	11 June 2013	New important identified risks, Important Potential risks & Important missing information are included	RMP is updated by including the new safety concerns.

Version	Date	Safety Concerns	Comment
		in the current RMP.	
Version 3.0	13 November 2013	Two safety concerns ("use in children under 7 years of age " & "Long-term safety data in children and adolescents") were included under missing information and updated throughout Parts III, V and VI to reflect these changes	RMP is updated by including additional safety concerns as per assessor assessment.