VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Generalised anxiety disorder

Generalised anxiety disorder (GAD) is an umbrella term that covers a wide range of anxiety disorders including panic disorder with or without agoraphobia (the fear of open spaces), post-traumatic disorder, obsessive disorder, social fears (phobia), and other specific phobias (arachnophobia i.e. the fear of spiders).

GAD is probably caused by abnormalities of certain neurotransmitters in the brain namely norepinephrine, dopamine, gamma-amino butyric acid and serotonin. GAD has also been linked to functional and structural changes in parts of the brain that are involved in the processing of emotions, especially fear and anxiety.

Patients with GAD often show magnified responses to fear and different stress stimuli which lead in an enhanced anxiety. These abnormal responses have been showed to settle upon psychological support and medication. The latter includes treatment with antidepressants such as SSRIs, SNRIs, TCAs, MAOI and others.[1-4]

Major depressive disorder

Depression is one of most common medical conditions and it is thought to be caused by a dysfunction of the neurotransmitters in the central nervous system, particularly serotonin, noradrenaline and dopamine. Risk factors for depression include adverse life events, hormonal changes, ill health, substance abuse, psychiatric illness etc. Major depression is usually diagnosed by having five or more of the following symptoms:

- Depressed mood
- Loss of interest or pleasure
- Significant weight change or appetite disturbance
- Sleep disturbance
- Agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness
- Diminished ability to think or concentrate
- Recurrent thoughts of death
- Suicide attempt, or specific plan for suicide

Major depressive disorder leads to increased mortality, including suicide, adverse outcomes of medical illness, disruption in interpersonal relationships, substance abuse, and lost work time. With appropriate management 70-80% of individuals diagnosed with major depressive disorder can achieve a significant reduction of symptoms.[5-7]

Diabetic peripheral neuropathic pain (Diabetic nerve pain)

Diabetic peripheral neuropathic pain is a common complication of either type 1 or type 2 diabetes and occurs when the patient's blood sugar levels are persistently high, causing damage to the peripheral nerves. This causes chronic pain in the limbs and foot ulcers.

Risk factors for diabetic neuropathy include smoking, alcohol, advanced age, poor control of blood glucose levels, hypertension, and ischaemic heart disease.

Signs and symptoms of diabetic nerve pain include sensation of tingling or burning in the limbs, sharp, stabbing pains in the hands and feet, difficulty walking, and difficulty exercising or even standing. Patients with diabetic nerve pain are advised to undergo routine medical check-ups and control their blood sugar levels more effectively. Lifestyle changes are also encouraged such as

quitting smoking and alcohol, exercising more and eating healthy foods. Treatment options include amitriptyline, pregabalin, duloxetine, nortriptyline, imipramine, lidocaine, tramadol and others.[8]

Stress urinary incontinence

Stress urinary incontinence is a common type of urinary incontinence. It occurs when urine is leaked upon applying pressure on the bladder when laughing, coughing, sneezing, exercising etc. This condition is caused by weakening of the pelvic floor muscles, the muscles that support the bladder. One of the most common causes of weakened pelvic floor muscles is childbirth. Other causes include obesity, advanced age and family history of urinary incontinence. Treatment options are pelvic floor exercises, dietary changes, surgery and medications such as duloxetine, antimuscarinic drugs such as tolterodine, and oxybutynin.[9]

VI.2.2 Summary of treatment benefits

Efficacy of duloxetine in major depressive disorder has been demonstrated in three studies. A total of 655 patients were given either duloxetine or placebo for the management of depressive symptoms. Different concentrations of duloxetine were given, ranging from 40mg daily to a maximum of 120mg daily and all studies concluded that duloxetine was significantly superior to placebo in managing depression.[10-12]

Duloxetine was superior to placebo for the treatment of diabetic neuropathic pain as seen in two publications. A total of 805 patients were assigned to placebo or duloxetine of different concentrations (20mg daily, 60mg daily, 120 daily) and the main finding was that duloxetine achieved better pain control in diabetic neuropathy compared to placebo.[13-14]

A study included 327 adult patients diagnosed with general anxiety disorders of which 168 were assigned to either duloxetine 60mg or 120mg and 159 were given dummy. Duloxetine treated patients showed a significant improvement and control of anxiety compared to dummy.[16]

A dummy-controlled study enrolled 458 women with stress urinary incontinence of which 231 were given placebo and 227 were given duloxetine 40mg in a twice daily regimen and treatment benefits were compared. The study results showed significant improvements in incontinence and quality of life with duloxetine compared to dummy drug.[15]

VI.2.3 Unknowns relating to treatment benefits

Based on the currently available data, no gaps in knowledge about efficacy in the target population were identified, that would warrant post-authorisation efficacy studies. Furthermore, there is no evidence to suggest that treatment results would be different in any subgroup of the target population, for any of the indications, taking into account factors such as age, sex, race or organ impairment.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Liver damage (Hepatic risks)	Cases of liver injury on duloxetine have been reported especially during the first months of treatment. Hepatitis, elevated liver enzymes and other liver dysfunctions are uncommon or rare adverse	Monitor for early symptoms of liver damage such as tiredness, dark urine, and yellow stools. Patients should consult their doctor before taking duloxetine if they are currently being

Risk	What is known	Preventability
	events of duloxetine therapy with incidences between 0.01% to 1%.	treated with another medicine which may cause liver damage.
Suicidal thoughts	Cases of suicidal thoughts/ ideation or attempt have been reported with antidepressants. Approximately 0.1% of patients will experience this adverse event. These side effects may be increased at the start of therapy.	Monitor patients with history of suicidal thoughts, ideation or attempt. Avoid administration of duloxetine in children as this patient group is at greater risk of deliberate self-harm. Avoid co-administration of duloxetine with other antidepressants. Monitor patients at the start of therapy for signs of suicidal ideation. Patients who have thoughts of harming or killing themselves at any time should contact their doctor or go to a hospital straight away.
High blood glucose (hyperglycaemia)	This may affect diabetic patients leading to poor blood glucose control and subsequent complications ie diabetic foot ulcers, peripheral neuropathy (a disorder of the nerves which can cause weakness, tingling or numbness) etc. Hyperglycaemia with duloxetine has an incidence between 0.01% and 1%.	Monitor blood glucose in patients at risk and adjust insulin requirements/ oral diabetic medication when necessary.
Steven-Johnson Syndrome (serious illness with blistering of the skin, mouth, eyes and genitals)	This is a rare side effect associated with duloxetine therapy with a prevalence of 0.1%.	Usually managed in an inpatient unit due to complex pathophysiology of the adverse event and possible clinical complications.
Bleeding in the gut (Gastrointestinal tract bleeding)	Duloxetine should not be given to patients with known bleeding tendencies or to patients on blood thinning medication, aspirin or other non-steroidal anti-inflammatory drugs as there is an increased risk of gastric bleeds.	Avoid co-administration of duloxetine with other medicines such as NSAIDs, or oral anticoagulants.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Cardiac toxicity (Cardiotoxicity) including those with concomitant administration of some medicines used to relieve pain and inflammation	Duloxetine has been associated with an increase in heart rate and blood pressure. This may subsequently cause a hypertensive crisis, a life-threatening event presenting with the following symptoms: chest pain, abnormal heart rhythm, headache, shortness of breath, vomiting, agitation etc. Patients at risk include those with diagnosed high blood pressure or any other disease affecting the heart or blood vessels. Duloxetine should not be used in patients with high blood pressure not controlled by medication.
Kidney damage (Renal failure)	Duloxetine should not be used in severe kidney impairment. However, no dosage adjustment is necessary in mild to moderate kidney disease. Adverse effects of duloxetine on the urinary system include renal disorders, decreased urine flow, abnormal urine odour.

Missing information

Risk	What is known
Side effects when used during pregnancy (Prospective data about potential risks of exposure to duloxetine during pregnancy)	Duloxetine should be avoided in pregnancy as the risks to the newborn babies are unknown. Duloxetine is not recommended during breast-feeding as very small amounts of the medicinal product have been found in breast milk.
Use of duloxetine 120mg in elderly patients	There is limited safety and efficacy data when administering 120mg duloxetine in elderly patients. Caution should be exercised in this patient group.

VI.2.5 Summary of risk minimisation measures by safety concern

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post-authorisation safety or efficacy studies are ongoing or are planned to be conducted for duloxetine.

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
1.0	30-07-2014	Identified risks: • Hepatic risks • Suicidality • Hyperglycaemia • Steven-Johnson Syndrome • Gastro-intestinal bleeding	New MA application for DCP

Version	Date	Safety Concerns	Comment
		• Serotonin syndrome Potential risks: • Renal failure • Cardiovascular events including in patients with concomitant use of NSAIDs • Upper gastro-intestinal bleeding with concomitant use of NSAIDs Missing information: • Use in pregnancy and lactation • Use in paediatric population • Use in elderly (>75 years) with concomitant use of NSAIDs • Long term use in chronic pain patients	
2.0	09-01-2015	<u>Identified risks:</u> • Hepatic risks • Suicidality • Hyperglycaemia • Steven-Johnson Syndrome • Gastro-intestinal tract bleeding <u>Potential risks:</u> • Renal failure • Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke) • Upper gastrointestinal tract (UGIT) bleeding events with concomitant use of NSAIDs <u>Missing information:</u>	Risk rephrased to be in line with reference product RMP, in relation to Preliminary Assessment Report received from Swedish Authorities dated 13 Nov 2014

Version	Date	Safety Concerns	Comment
		• Prospective data about potential risks of exposure to duloxetine during pregnancy • Characterization of the safety and tolerability of duloxetine in paediatric patients • Safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use	
3.0	08-02-2015	<u>Identified risks:</u> • Hepatic risks • Suicidality • Hyperglycaemia • Steven-Johnson Syndrome • Gastro-intestinal tract bleeding • Serotonin syndrome <u>Potential risks:</u> • Renal failure • Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke) • Upper gastrointestinal tract (UGIT) bleeding events with concomitant use of NSAIDs <u>Missing information:</u> • Prospective data about potential risks of exposure to duloxetine during pregnancy • Characterization of the safety and tolerability of duloxetine in paediatric patients • Safety of duloxetine in elderly patients ≥75 years old with	Serotonin syndrome added as an important identified risk as per originator's summary of safety concerns

Version	Date	Safety Concerns	Comment
		concomitant NSAIDs use	
4.0	21-05-2015	Identified risks: • Hepatic risks • Suicidality • Hyperglycaemia • Steven-Johnson Syndrome • Gastro-intestinal tract bleeding Potential risks: • Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke) • Renal failure Missing information: • Prospective data about potential risks of exposure to duloxetine during pregnancy • Use of duloxetine 120mg in the elderly	Originator's summary of safety concerns has been updated following assessment of PSUSA. The summary table of safety concerns has been updated accordingly