5.2 Part VI.2 Elements for a Public Summary

The following applies to Duloxetine strengths, 30 mg and 60 mg hard gastro-resistant capsules.

5.2.1 Part VI.2.1 Overview of disease epidemiology

Neuropathic pain

The proportion of people (prevalence) with neuropathic pain was estimated to be 6% to 8%. A study in the Netherlands estimated the annual incidence (rate at which an event occurs, as the number of new cases of a specific disease occurring during one year in a population) of neuropathic pain in the general population to be almost 1%. Painful diabetic neuropathy is estimated to affect 16% to 26% of diabetics.

The prevalence of chronic pain after surgery is is estimated to be in the range of 10% to 50%.. Pain is severe in 2% to 10% of these patients, and several clinical features resemble those of neuropathic pain. [NICE Clinical Guideline, 2013]

Depression

Depression is estimated to affect 350 million people in all communities across the world. Depressive disorders often start at a young age; they reduce people's functioning and are often recurring. Depression is the leading cause of disability worldwide in terms of total years lost due to disability. The demand for curbing depression and other mental health conditions is on the rise globally.

Signs and symptoms of depression include depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Moreover, depression often comes with symptoms of anxiety. At its worst, depression can result in suicide. Almost 1 million lives are lost yearly due to suicide (3000 suicide deaths per day). For every person who completes suicide, at least 20 may attempt suicide.

The burden of depression is 50% higher in females than males.. [WHO, 2012]

Generalized Anxiety Disorder

Generalized anxiety disorder (GAD) is characterized by excessive and persistent worrying that is hard to control, causes significant distress or impairment, and occurs on more days than not for at least six months. Other features include apprehensiveness,irritability, fatigue and muscular tension.

GAD is common in community and clinical settings. Studies in the United States found a lifetime prevalence (total number of cases of a disease in a given population at a specific time) of GAD of 5.1%[Wittchen HU, Zhao S, Kessler RC, Eaton WW, 1994], [Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE, 2005] to 11.9%[Kessler RC, Gruber M, Hettema JM, Hwang I, Sampson N, Yonkers KA, 2008]. Studies in Europe found a 12-month prevalence of 1.7% to 3.4% [Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen HC, 2011], and a lifetime prevalence of 4.3% to 5.9% [Wittchen HU, Jacobi F, 2005].

In a study of adult patients in four Nordic countries, rates of GAD were 4.1% to 6.0% in men, and 3.7 % to 7.1 % in women [Munk-Jørgensen P, Allgulander C, Dahl AA, Foldager L, Holm M, Rasmussen I, Virta A, Huuhtanen MT, Wittchen HU, 2006].

5.2.2 Part VI.2.2 Summary of treatment benefits

For major depression, Duloxetine was compared with placebo (a dummy treatment) in studies involving a total of 2,544 patients. Duloxetine was more effective than placebo in four studies. In two studies where the approved dose of Duloxetine was compared with placebo, Duloxetine was more effective. For neuropathic pain, Duloxetine was compared with placebo in two studies. These studies

showed that Duloxetine was more effective at reducing pain than placebo, and pain reduction was seen from the first week of treatment for up to 12 weeks.

For generalised anxiety disorder, Duloxetine was compared with placebo in five studies involving a total of 2,337 patients. Duloxetine was shown to be more effective than placebo at treating the disorder and preventing symptoms returning.

5.2.3 Part VI.2.3 Unknowns relating to treatment benefits

Duloxetine should not be used in patients under 18 years as its benefit has not been demonstrated.

Data on use of Duloxetine 120 mg in elderly patients with major depressive disorders and generalised anxiety disorder are limited. Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. The safety of duloxetine in infants is not known. The safety and efficacy of duloxetine for the treatment of diabetic peripheral neuropathic pain or generalized anxiety disorder have not been studied. No data are available.

5.2.4 Part VI.2.4 Summary of safety concerns

Table 4-5 Important identified risks

Risk	What is known	Preventability
Hepatic risks (liver damage)	Duloxetine must not be used in patients with liver disease resulting in hepatic impairment	Close monitoring of liver function is advised.
Suicidality (thought of suicide)	If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer. You may be more likely to think like this if you: • have previously had thoughts about killing or harming yourself • 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	If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.
Hyperglycemia (high blood sugar levels)	Duloxetine might increase the blood sugar levels.	Regular blood checks for blood glucose levels.
Stevens-Johnson Syndrome (life-threatening skin condition)	In rare cases, Stevens-Johnson Syndrome might occur during treatment with duloxetine.	Caution is advised and immediate medical treatment in case the symptoms of Stevens-Johnson Syndrome occur (fever, sore throat, and fatigue – in the

Risk	What is known	Preventability
		beginning - a rash of round lesions about an inch across arises on the face, trunk, arms and legs, and soles of the feet, but usually not the scalp)
Gastrointestinal Tract Bleeding (bleeding in the stomach, bowels)	There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs), including duloxetine.	Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid (ASA)), and in patients with known bleeding tendencies.
Serotonin syndrome (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles)	Concomitant treatment with duloxetine and other serotonergic agents like Triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), SNRIs (such as venlafaxine), tricyclic antidepressants (such as clomipramine, amitriptyline), pethidine, St John's Wort and MAOIs (such as moclobemide and linezolid) increase the risk of Serotonin syndrome.	If concomitant treatment with Duloxetine and other serotonergic agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Table 4-6 Important potential risks

Risk	What is known
Cardiovascular events (heart problems) including those with concomitant use of NSAIDs – anti-inflammatory medication - (including myocardial infarction, heart failure, and stroke)	Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. Caution should also be exercised when duloxetine is used with medicinal products that may impair its metabolism. For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered. In patients with uncontrolled hypertension duloxetine should not be initiated
Upper gastrointestinal tract (UGIT) bleeding events with concomitant use of NSAIDs	There are no adequate data on the use of duloxetine in pregnant women. Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Safety of duloxetine in infants is not known, therefore, the use of Duloxetine while breast-feeding is not

Risk	What is known
	recommended.
Renal Failure (serious kidney condition)	Duloxetine must not be used in patients with severe renal impairment.

Table 4-7 Missing information

Risk	What is known
Characterization of the safety and tolerability of duloxetine in pediatric patients	Duloxetine should normally not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behavior and anger) when they take this class of medicines. Despite this, your doctor may prescribe Duloxetine for patients under 18 because he/she decides that this is in their best interests. If your doctor has prescribed Duloxetine for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any of the symptoms listed above develop or worsen when patients under 18 are taking Duloxetine. Also, the long-term safety effects concerning growth, maturation, and cognitive and behavioral development of Duloxetine in this age group have not yet been demonstrated.
Prospective data about potential risks of exposure to duloxetine during Pregnancy	There are no adequate data on the use of duloxetine in pregnant women. Duloxetine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Safety of duloxetine in infants is not known, therefore, the use of Duloxetine while breast-feeding is not recommended. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Characterization of drug utilization in unapproved indications and populations	There are no adequate data on the use of duloxetine in unapproved indications and populations.
Safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use	Data on the use of duloxetine 120 mg in elderly patients with major depressive disorders and generalised anxiety disorder are limited. Therefore, caution should be exercised when treating the elderly with the maximum dosage.
Long-term safety data in chronic pain patients	No data of the safety of duloxetine for the treatment of diabetic peripheral neuropathic pain (pain which is caused by peripheral nerve damage due to diabetes) are available.

5.2.5 Part VI.2.5 Summary of additional risk minimization 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.

5.2.6 Part VI.2.6 Planned post authorization development plan

None

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

Not applicable (first submission)