VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Incidence and prevalence of target indication	Major depressive disorder (MDD) is a mental disorder characterized by a pervasive and persistent low mood which is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities. Major depressive disorder is a disabling condition that adversely affects a person's family, work or school life, sleeping and eating habits, and general health. It is believed to currently affect approximately 298 million people as of 2010 (4.3% of the global population). Lifetime prevalence varies widely, from 3% in Japan to 17% in the US and 8.56% in Europe, where the prevalence is 10.05% for women and 6.61% for men. In the United States, around 3.4% of people with major depression commit suicide, and up to 60% of people who commit suicide had depression or another mood 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. Diabetic peripheral neuropathic pain (DPNP) affects approximately 11 % of patients with diabetic peripheral neuropathy, which is estimated to be present in 50 % of people living with diabetes mellitus. Patients suffering from DPNP have chronic, painful symptoms that diminish their quality of life, disrupt sleep, and can lead to depression. Stress urinary incontinence (SUI) is losing urine without meaning to during physical activity, such as coughing, sneezing, laughing, or exercise. The prevalence ranges from 25 to 51 percent and is relatively low early in life, has a peak around the time of menopause, and then rises steadily between the ages of 60 and 80 years.

VI.2.2 Summary of treatment benefits

For the treatment of major depressive disorder, duloxetine has been compared with placebo in eight main studies involving a total of 2,544 patients. Although the results of the depression studies varied, duloxetine was more effective than placebo in reducing the patients' symptoms in all of the studies and it also took longer for symptoms to return in patients taking duloxetine than in those taking placebo.

For the treatment of neuropathic pain, duloxetine has been compared with placebo in two 12-week studies in 809 diabetic adults. For the treatment of diabetic neuropathic pain, duloxetine was more effective at reducing the severity of pain than placebo and pain reduction was seen from the first week of treatment for up to 12 weeks.

For the treatment of generalised anxiety disorder, duloxetine has been compared with placebo in five studies involving a total of 2,337 patients. Duloxetine was more effective than placebo at treating the disorder by measuring the reduction in symptoms after nine to 10 weeks and preventing symptoms returning.

Duloxetine has been studied in a total of 2,850 women with stress urinary incontinence. The four main studies involved 1,913 women and lasted 12 weeks, comparing duloxetine (mostly as 40 mg twice daily) with placebo. In all four studies, the patients treated with duloxetine had fewer episodes of incontinence after 12 weeks, with about four or five fewer episodes of

incontinence per week, in comparison with the number before the study. The incontinence episode frequency decreased by 52% in the duloxetine group, compared with a decrease of 33% in the placebo-treated group. The incontinence-specific quality-of-life questionnaire scores were also improved in the duloxetine group. Duloxetine was more effective than placebo only in patients who had more than 14 incontinence episodes per week (moderate to severe SUI) at the start of the study.

VI.2.3 Unknowns relating to treatment benefits

Not applicable. This is a generic medicine and its benefits and risks are taken as being the same as of innovator's product.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Liver damage (Hepatic risk)	In up to 1 in 100 people duloxetine has been associated with the developing of inflammation of the liver that may cause abdominal pain and yellowing of the skin or whites of the eyes (jaundice). Rarely, up to 1 in 1000 people, duloxetine can cause liver failure.	You must not take this medication if you have liver disease and if you are currently being treated with another medicine which may cause liver damage, this medicine may not be suitable for you. If you get any side effects, talk to your doctor or pharmacist.

Wanting to kill yourself (Suicidality)	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.** You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.
Increases in blood sugar (Hyperglycemia)	Your medicine may cause effects that you may not be aware of, such as increases in blood levels of sugar.	Your doctor may periodically check your blood.
Serious illness with blistering of the skin, mouth, eyes and genitals (Stevens-Johnson Syndrome)	Rarely, up to 1 in 1000 people, duloxetine has been associated with the developing of Stevens-Johnson syndrome, a serious illness with blistering of the skin, mouth, eyes and genitals.	If you get any side effects, talk to your doctor or pharmacist.
Bleeding from the mouth, oesophagus, stomach or bowels (Gastrointestinal Tract Bleeding)	There have been reports of various bleeding abnormalities and therefore caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function and in patients with known bleeding tendencies.	If you have a history of bleeding disorders (tendency to develop bruises), this medicine may not be suitable for you. You should also tell your doctor if you are taking medicines which thin the blood or prevent the blood from clotting as these medicines might increase the risk of bleeding.

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
Heart and blood vasculature-related events including those with concomitant use of NSAIDs (Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke))	Duloxetine has been associated with an increase in blood pressure, including cases of life-threatening increases in blood pressure (hypertensive crisis), that has been associated with irreversible organ damage, especially in patients with preexisting hypertension. Blood pressure monitoring is recommended, especially during the first month of treatment. Talk to your doctor if you have high blood pressure or heart disease. Your doctor will tell you if you should be taking this medicine
Bleeding from the mouth, oesophagus, stomach or duodenum (Upper gastrointestinal tract (UGIT) bleeding events with concomitant use of NSAIDs)	There have been reports of various bleeding abnormalities. Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function, and in patients with known bleeding tendencies. If you have a history of bleeding disorders (tendency to develop bruises), this medicine may not be suitable for you. You should also tell your doctor if you are taking medicines which thin the blood or prevent the blood from clotting as these medicines might increase the risk of bleeding.
Impaired kidney function (Renal Failure)	The relatedness of risk of renal failure to duloxetine administration has not been confirmed yet. However, if you have kidney disease, this medicine may not be suitable for you.

Missing information:

Risk	What is known
Potential risks of exposure to duloxetine during pregnancy	There are no adequate well-controlled trials in pregnant women and therefore duloxetine should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus. Discontinuation symptoms in the newborn may occur if the mother is taking the medicine near term. The medicine is weakly excreted into human milk therefore the patients are advised not to breastfeed if they are taking duloxetine.
Safety of duloxetine in elderly patients ≥ 75 years old with concomitant NSAIDs use	Safety in elderly patients who are using NSAIDs concomitantly has not been evaluated as of yet.
Characterization of the safety and tolerability of duloxetine in children and adolescents (Characterization of the safety and tolerability of duloxetine in pediatric patients)	Duloxetine should normally not be used in children and adolescents under the age of 18 years for the treatment of major depressive disorder because of safety and efficacy concerns. The safety and efficacy of duloxetine for the treatment of diabetic peripheral neuropathic pain, generalized anxiety disorder or stress urinary incontinence have not been studied. No data are available.

VI.2.5 Summary of additional risk minimisation 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.

The Summary of Product Characteristics and the Package leaflet for this product can be found at the national agencys' webpages.

This is a generic application and there are no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable. No postauthorisation studies are planned.

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

Not applicable, this is the first Risk management plan.