VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Major depressive disorder (MDD)

Major depressive disorder (MDD) is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities. Chemical changes in the brain are believed responsible for this illness that may be due to a problem with person genes or may be triggered by certain stressful events. More likely, it is a combination of both.

The Western European countries 12-month occurrence rate is around 5%, with higher prevalence in women, the middle-aged, less privileged groups, and those experiencing social adversity.

The US 12-month respective rate in adults is 6.7% . The frequency in 18- to 29-year-old individuals is threefold higher than the frequency in those aged 60 or older. The occurrence rates appear to be unrelated to ethnicity, education, income, or marital status. In childhood, boys and girls are equally affected. However, in adolescence and adulthood, the frequency is 1.5- to 3-fold higher in females compared to males.

Diabetic Peripheral Neuropathic Pain (DPNP)

Peripheral neuropathy, also called distal symmetric neuropathy or sensorimotor neuropathy, is nerve damage in the arms and legs. Feet and legs are likely to be affected before hands and arms. About 60-70% of people with diabetes have some form of neuropathy. People with diabetes can develop nerve problems at any time, but risk rises with age and longer duration of diabetes. The highest rates of neuropathy are among people who have had diabetes for at least 25 years. Diabetic neuropathies also appear to be more common in people who have problems controlling their blood glucose, also called blood sugar, as well as those with high levels of blood fat and blood pressure and those who are overweight.

In a landmark study, over 4400 patient with diabetes were serially evaluated over 25 years.

Neuropathy was defined as decreased sensation in the feet and depressed or absent ankle reflexes.

The onset of neuropathy correlated positively with the duration of diabetes and, by 25 years, 50 percent of patients had neuropathy

Generalized anxiety disorder (GAD)

Generalized anxiety disorder (GAD) is a long-term condition that causes patient to feel anxious about a wide range of situations and issues, rather than one specific event.

People with GAD feel anxious most days and often struggle to remember the last time they felt relaxed. GAD can cause both mental and physical symptoms. These vary from person to person, but can include feeling restless or worried and having trouble concentrating or sleeping. In Europe, studies suggest that GAD is a relatively rare disorder in the community with a 12-month frequency of about 2%, with a higher incidence in women and most common among older age groups.

Nevertheless, GAD affects about 3.1% American adults age 18 years and older (about 18%) in a given year. The average age of onset is 31 years old. GAD affects about 6.8 million American adults,

including twice as many women as men. The disorder develops gradually and can begin at any point in the life cycle, although the years of highest risk are between childhood and middle age.

VI.2.2 Summary of treatment benefits

Depression is commonly associated with physical or painful symptoms.
Serotonin and norepinephrine appear to be involved in the mechanisms of both depression and pain, and these conditions may be mediated through a common pathway. Antidepressants that act via serotonergic or noradrenergic mechanisms (or both) have analgesic properties independent of their effects on mood and have been used successfully to manage the symptoms of various pain states.
Duloxetine, a dual-acting appear to possess analgesic efficacy similar to that of the tricyclic antidepressants (TCAs), but have a more favorable safety and tolerability profile. In addition it has an efficacy advantage over selective serotonin reuptake inhibitors (SSRIs) in treating the painful physical symptoms of depression and in achieving remission of all symptoms of depression.

Studies suggest that ***diabetic peripheral neuropathic pain*** is related to an unbalanced release of norepinephrine and serotonin from neurons. Serotonin-norepinephrine reuptake inhibitors (SNRIs), including venlafaxine and duloxetine, are a category of antidepressants for treatment of diabetic peripheral neuropathic pain. They are better tolerated and have fewer drug interactions than tricyclic antidepressants (TCAs).

VI.2.3 Unknowns relating to treatment benefits

Duloxetine should not be used in children and adolescents aged < 18 years. There is no evidence for its use in this population and antidepressants increase the risk of suicidal thinking and behaviour in children, adolescents and young adults.

There are no adequate data on the use of duloxetine in pregnant women. The potential risk of reproductive toxicity for humans is unknown.

There is no data available on the safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use.

VI.2.4 Summary of safety concerns

Important identified risks		
Risk	**What is known**	**Preventability**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
Liver disease *(Hepatic risks)*	Duloxetime undergoes predominantly hepatic metabolism (via two cytochrome P450 isozymes,	Duloxetine must not be used in patients with liver disease.

	CYP2D6 and CYP1A2). Circulating metabolites are pharmacologically inactive. However, moderate liver diseases affect pharmacokinetics of duloxetine. In patients with liver problems plasma clearance of duloxetine is lower than in healthy patients. Thus, use of duloxetine in patients with liver diseases may result in hepatic impairment.	Physician should be aware if patient has liver problems
Thoughts of harming or killing yourself *(Suicidality)*	Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. 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	Close supervision of patients and in particular those at high risk should accompany medicinal product therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.
High blood sugar *(Hyperglycaemia)*	Hyperglycaemia has been reported uncommonly, especially in diabetic patients (may affect up to 1 in 100 people)	Blood sugar level in patient with diabetic neuropathy pain should be monitored
Serious allergic reaction *(Stevens-Johnson Syndrome)*	Stevens-Johnson syndrome is a serious illness with blistering of the skin, mouth, eyes and genitals. Based on the post-marketing surveillance of duloxetine adverse events it may occur rarely (may affect up to 1 in 1000 people)	Duxoletine administration should be discontinued immediately if Stevens-Johnson syndrome symptoms occur. Patient should ask physician advice
Loss of blood in the gastrointestinal tract (from the pharynx to the rectum)	There have been reports of bleeding abnormalities, such as ecchymoses, purpura and gastrointestinal haemorrhage with selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake	Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (e.g. NSAIDs or acetylsalicylic acid

(Gastrointestinal Tract Blending)	inhibitors (SNRIs), including duloxetine. Adverse events such as gastrointestinal haemorrhage, haematochezia (black tarry stools) have been reported on the post-marketing surveillance of duloxetine adverse events	(ASA)), and in patients with known bleeding tendencies.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential r isk)**
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 and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. 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. 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.
Upper gastrointestinal tract (UGIT) blending events with concomitant use of NSAIDs	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.
Renal failure	No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min).

	However, increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). Duloxetine must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min)

Important missing information	
Risk	**What is known**
Characterization of the safety and tolerability of duloxetine in paediatric patients	Duloxetine should 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 generalised anxiety disorder in paediatric patients aged 7-17 years have not been established. The safety and efficacy of duloxetine for the treatment of diabetic peripheral neuropathic pain has not been studied. No data are available. Current available data *Use in children and adolescents under 18 years of age* [Product name should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (suicide attempts 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 (please refer to *'clinical efficacy and safety'* below). In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking. *Adverse events in paediatric population* A total of 509 paediatric patients aged 7 to 17 years with major depressive disorder and 241 paediatric patients aged 7 to 17 years with generalised anxiety disorder were treated with duloxetine in clinical trials. In general, the adverse reaction profile of duloxetine in children and adolescents was similar to that seen for adults. A total of 467 paediatric patients initially randomized to duloxetine in clinical trials experienced a 0.1 kg mean decrease in weight at 10-weeks compared with a 0.9 kg mean increase in 353 placebo-treated patients. Subsequently, over the four- to six-month extension period, patients on average trended toward recovery to their expected baseline

	weight percentile based on population data from age- and gender-matched peers. In studies of up to 9 months an overall mean decrease of 1% in height percentile (decrease of 2% in children (7-11 years) and increase of 0.3% in adolescents (12-17 years)) was observed in duloxetine-treated paediatric patients *Clinical efficacy and safety* Duloxetine has not been studied in patients under the age of 7. Two randomized, double-blind, parallel clinical trials were performed in 800 paediatric patients aged 7 to 17 years with major depressive disorder. These two studies included a 10 week placebo and active (fluoxetine) controlled acute phase followed by six months period of active controlled extension treatment. Neither duloxetine (30-120 mg) nor the active control arm (fluoxetine 20-40 mg) statistically separated from placebo on change from baseline to endpoint in the Children´s Depression Rating Scale-Revised (CDRS-R) total score. Discontinuation due to adverse events was higher in patients taking duloxetine compared with those treated with fluoxetine, mostly due to nausea. During the 10-week acute treatment period, suicidal behaviours were reported (duloxetine 0/333 [0%], fluoxetine 2/225 [0.9%], placebo 1/220 [0.5%]). Over the entire 36-week course of the study, 6 out of 333 patients initially randomized to duloxetine and 3 out of 225 patients initially randomized to fluoxetine experienced suicidal behaviour (exposure adjusted incidence 0.039 events per patient year for duloxetine, and 0.026 for fluoxetine). In addition, one patient who transitioned from placebo to duloxetine experienced a suicidal behaviour while taking duloxetine. A randomised, double-blind, placebo-controlled study was performed in 272 patients aged 7-17 years with generalised anxiety disorder. The study included a 10 week placebo-controlled acute phase, followed by an 18 week extension treatment period. A flexible dose regimen was used in this study, to allow for slow dose escalation from 30 mg once daily to higher doses (maximum 120 mg once daily). Treatment with duloxetine showed a statistically significantly greater improvement in GAD symptoms, as measured by PARS severity score for GAD (mean difference between duloxetine and placebo of 2.7 points [95% CI 1.3-4.0]), after 10 weeks of treatment. The maintenance of the effect has not been evaluated. There was no statistically significant difference in discontinuation due to adverse events between duloxetine and placebo groups during the 10 week acute treatment phase. Two patients who transitioned from placebo to duloxetine after the acute phase experienced suicidal behaviours while taking duloxetine during the extension phase. A conclusion on the overall benefit/risk in this age group has not been established

Prospective data about potential risks of exposure to duloxetine during pregnancy	There are no adequate data on the use of duloxetine in pregnant women. Studies in animals have shown reproductive toxicity at systemic exposure levels (AUC) of duloxetine lower than the maximum clinical exposure (please refer to the *'preclinical safety data'* below). The potential risk for humans is unknown. Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with duloxetine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin). As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth. [Product name] should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy. *Preclinical safety data* Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine (45 mg/kg/day) before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In prenatal/postnatal toxicity studies in

	the rat, duloxetine induced adverse behavioural effects in the offspring at exposures below maximum clinical exposure (AUC). Studies in juvenile rats reveal transient effects on neurobehaviour, as well as significantly decreased body weight and food consumption; hepatic enzyme induction; and hepatocellular vacuolation at 45 mg/kg/day. The general toxicity profile of duloxetine in juvenile rats was similar to that in adult rats. The no-adverse effect level was determined to be 20 mg/kg/day
Safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use	There is no data available on the safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use.

VI.2.5 Summary of 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.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Not applicable

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Change
1.0	18.07.2014	**Important identified risks** • Hepatic risks • Elevated plasma concentrations of duloxetine in co-administration with potent CYP1A2 inhibitors • Serotonine syndrome due to co-administration with nonselective, irreversible monoamine oxidase inhibitors (MAOIs) • Suicidality • Hyperglycemia, Hyponatraemia • Stevens-Johnson Syndrome • Gastrointestinal Blending (GIT bending)	Initial version

		Important potential risks • Mydriasis • Cardiovascular events (including myocardial infarction and ventricular arrhythmia) • Upper gastrointestinal blending events with concomitant use of NSAIDs • Renal failure • Akathisia/ psychomotor restlessness **Missing information** • Lack of data on the safety and tolerability of duloxetine in paediatric patients • Absence of data about potential risks of exposure to duloxetine during pregnancy • Characterization of drug utilization in unapproved indications and populations	
2.0	08.04.2015	**Important identified risks** • Hepatic risks • Suicidality • Hyperglycemia • Stevens-Johnson Syndrome • Gastrointestinal Tract Blending **Important potential risks** • Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure, and stroke) • Upper gastrointestinal tract (UGIT) blending events with concomitant use of NSAIDs • Renal failure **Missing information** • Characterization of the safety and tolerability of duloxetine in paediatric patients • Prospective data about potential risks of exposure to duloxetine during pregnancy	Implementation of day70+day100 assessors comments

		• Safety of duloxetine in elderly patients ≥75 years old with concomitant NSAIDs use	