VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Major depressive disorder (MDD) has been identified as the fourth most disabling illness in the world. Of those individuals with an episode of MDD it has been indicated that 41% will have a second episode within a year, 59% within 2 years and 74% within 5 years.

Many available options exist for the treatment of mood disorders. The treatment of depression is commonly divided into three distinct phases. Specific objectives of each treatment phase provide a strategic map for managing these patients. The acute phase begins with the initial presentation of an episode and is designed to elicit at least a response as determined by a clinically significant reduction in symptoms. This is followed by a continuation phase designed to prevent a relapse of the most recent episode. Continuation therapy of at least 6 months is now recommended. Complete symptom remission can occur in either the acute or continuation phase, and full recovery is defined as a sustained period of remission lasting several months. The final phase is maintenance treatment, which has as its goal the prevention of a new acute episode (a recurrence) of major depressive disorder.Maintenance treatment has specifically been recommended for any patient who has had three or more major depressive episodes in the past 5 years.

Diabetic peripheral neuropathic pain.

Peripheral neuropathy is a common complication of diabetes mellitus, occurring in 30 to 50 percent of patients with the disease. It involves the loss of sensation in a symmetric stocking-and-glove distribution, starting in the toes and progressing proximally. Approximately 10 to 20 percent of patients with diabetes have diabetic peripheral neuropathic pain, which is a burning, tingling, or aching discomfort that worsens at night.

Generalized Anxiety Disorder (GAD)

Is one of the most common anxiety disorders seen in general medical practice and is characterized by excessive, exaggerated anxiety and worry about everyday life events with no obvious reasons for worry. The disorder has an estimated current prevalence in general medical practice of 2.8% to 8.5% and in the general population of 1.6% to 5.0%.

VI.2.2 Summary of treatment benefits

Duloxetine hydrochloride is a combined serotonin and noradrenaline reuptake inhibitor. This antidepressant drug is a potent dual reuptake inhibitor of serotonin (5- HT) and norepinephrine (NE), but with lacks of significant affinity for muscarinic, histaminergic, a/adrenergic, dopaminergic, serotonergic and opioid receptors.

Although the results of the depression studies varied, duloxetine hydrochloride was more effective than placebo in four of the studies. In the two studies where the approved dose of duloxetine hydrochloride was compared with placebo, duloxetine hydrochloride was more effective. It also took longer for symptoms to return in patients taking duloxetine hydrochloride than in those taking placebo.

For the treatment of diabetic neuropathic pain, duloxetine hydrochloride was more effective at reducing pain than placebo. In both studies, pain reduction was seen from the first week of treatment for up to 12 weeks.

For generalised anxiety disorder, duloxetine hydrochloride was also more effective than placebo at treating the disorder and preventing symptoms returning.

VI.2.3 Unknowns relating to treatment benefits

There are no relevant unknowns relating to treatment benefits.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Suicidal thoughts and behaviour	Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.	Patients being treated with Duloxetine PI Ltd. should be observed closely for clinical worsening, suicidality, and unusual changes in behaviour, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. Such observation would generally include at least weekly face-to-face contact with patients or their family members or caregivers during the first 4 weeks of treatment.
Hepatic risks	Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine. Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular.	Patients with pre-existing liver disease should not take Duloxetine PI Ltd. Duloxetine PI Ltd. should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Risk	What is known	Preventability
Gastrointestinal tract bleeding	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.	Patients should tell their doctor or pharmacist if they have a history of bleeding disorders (tendency to develop bruises), gastrointestinal bleeding or are treated with medicines which thin the blood or prevent the blood from clotting (oral anticoagulants or antiplatelet agents) as these medicines might increase the risk of bleeding.
Hyperglycaemia	In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA1c was stable in both duloxetine-treated and placebo-treated patients. There was also a sm all increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.	Patients should tell their doctor or pharmacist if they suffer from diabetes or glucose intolerance or are treated with medicines which can increase the level of blood sugar such as glucocorticoids.
Stevens-Johnson syndrome	Stevens-Johnson syndrome (serious illness with blistering of the skin, mouth, eyes and genitals), serious allergic reaction which causes swelling of the face or throat (angioedema) might be connected with duloxetine use with the frequency rare (≥1/10,000 to <1/1,000),	Patients should tell their doctor or pharmacist if they suffer from any hypersensitivity or start suffering from blistering of the skin, mouth, eyes, genitals or hypersensitivity manifested as swelling of the face or throat after Duloxetine PI Ltd. administration.

Risk	What is known (Including reason why it is considered a potential risk)
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 PI Ltd. should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure. 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 bleeding 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 of Duloxetine PI Ltd. is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Duloxetine PI Ltd. must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min) or patients on hemodialysis.

Important missing information

Risk	What is known
Elderly patients ≥ 75 years old with concomitant use of NSAIDs use	Tolerability of duloxetine 60 mg once daily in elderly patients (≥65 years) was comparable to that seen in the younger adults. However, data on elderly patients exposed to the maximum dose (120mg per day) are limited and thus, caution is recommended when treating this population.

Risk	What is known
Prospective data about potential risks of exposure to duloxetine during Pregnancy	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. 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. 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. Duloxetine PI Ltd. 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.
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 diabetic peripheral neuropathic pain or generalized anxiety disorder have not been studied. No data are available.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a S ummary 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 medicinal product can be found in the competent authority's webpage.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No post authorisation development plan was proposed.

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

Table 2. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
01.00	23-June-2014	**Identified risks :** • Serotonin symdrome • Suicidal thoughts and behaviour • Withdrawal reactions. • Hepatic impairment • Haemorrhage • Uncontrolled Hypertension • Drug interactions withpotent CYP1A2 inhibitors • Drug interactions with nonselective, irreversible Monoamine oxidase inhibitors (MAOIs) • Drug interactions with CNS medicinal products • Drug interactions with medicinal products metabolised by CYP2D6 • Drug interactions with anticoagulants and antiplatelet agents • Severe renal impairment **Potential risks :** • Agggression	Initial version.

Version	Date	Safety Concerns	Comment
		• Orthostatic hypotension • Mania • Seizures • Intraocular pressure • Acute narrow-angle glaucoma. • Increased heart rate • Pre-existing hypertension • Drug interaction with St jon's wort • Hepatitis /liver laboratory abnormalities • Increase risk for hyponatraemia • Psychomotor restlessness **Missing information:** • Use in pregnancy and lactation • Use in children under 18 year of age • Use in elderly patients	
v.2.0	19-Jan-2015	**Identified risks :** • Suicidal thoughts and behaviour • Hepatic risks • Gastrointestinal tract bleeding • Hyperglycaemia • Stevens-Johnson syndrome	D 70 RMS comments

Version	Date	Safety Concerns	Comment
		Potential risks : • Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure and stroke) • Upper gastrointestinal tract bleeding events with concomitant use of NSAIDs • Renal failure **Missing information:** • Elderly patients ≥ 75 years old with concomitant use of NSAIDs use • Prospective data about potential risks of exposure to duloxetine during Pregnancy • Long-term safety data in chronic pain patients	
v.3.0	20-May-2015	**Identified risks :** • Suicidal thoughts and behaviour • Hepatic risks • Gastrointestinal tract bleeding • Hyperglycaemia • Stevens-Johnson syndrome	D 120 RMS comments

Version	Date	Safety Concerns	Comment
		Potential risks : • Cardiovascular events including those with concomitant use of NSAIDs (including myocardial infarction, heart failure and stroke) • Upper gastrointestinal tract bleeding events with concomitant use of NSAIDs • Renal failure **Missing information:** • Elderly patients ≥ 75 years old with concomitant use of NSAIDs use • Prospective data about potential risks of exposure to duloxetine during Pregnancy • Characterization of the safety and tolerability of duloxetine in paediatric patients	