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Summary of the risk management plan (RMP) for Duloxetine Mylan (duloxetine)

This is a summary of the risk management plan (RMP) for Duloxetine Mylan, which details the measures to be taken in order to ensure that Duloxetine Mylan is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Duloxetine Mylan, which can be found on Duloxetine Mylan's EPAR page.

Overview of disease epidemiology

Duloxetine Mylan is a medicine that is used to treat adults with the following diseases:

Major depressive disorder

Major depressive disorder or major depression is a disease where a person has persistent low mood or loss of interest in things they used to enjoy. In addition the person may experience loss of energy or changes in appetite and sleep.

Estimates in various countries across the world (Belgium, France, Germany, Italy, the Netherlands, Spain, and the United States) suggest that approximately 17.5% of people have major depressive disorder.

Diabetic peripheral neuropathic pain

Diabetic peripheral neuropathic pain is pain that results from damage to nerve endings in the extremities and is caused by diabetes.

Approximately 16% to 26% of people with diabetes have diabetic peripheral neuropathic pain.

Generalised anxiety disorder

Generalised anxiety disorder is long-term anxiety or nervousness about everyday matters. The cause of generalised anxiety disorder is not clear although it is believed to be related to both genetic factors and life experiences.

The number of people affected by this condition varies between different countries and cultures. Regardless of geography, however, women are more likely to be affected than men. There also appear to be more cases of generalised anxiety disorder among older people up until the age of 60, when the number of cases begins to decline. Among those aged 18 to 64 years, it is estimated that 6.2% (7.7% of women and 4.6% of men) will have generalised anxiety disorder over their lifetimes.

Summary of treatment benefits

Duloxetine Mylan contains the active substance duloxetine. It is available as capsules (30 and 60 mg) and is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Cymbalta.

Because Duloxetine Mylan is a generic medicine, its benefits and risks are taken as being the same as the reference medicine's. Studies in people have been limited to tests to determine that it is bioequivalent to the reference medicine, Cymbalta. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

Unknowns relating to treatment benefits

Duloxetine Mylan should not be used in patients under 18 years old. Duloxetine has not been studied in patients under the age of 7. In children with depression aged 7 to 17 years two studies carried out in 800 patients showed an increased risk of side effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger).

Duloxetine for the treatment of diabetic peripheral neuropathic pain or generalised anxiety disorder has not been studied in children.

Moreover, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

The safety of duloxetine in infants is not known. Therefore, the use of Duloxetine Mylan while breastfeeding is not recommended.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Problems with the liver (Hepatic risks)	Side effects affecting the liver such as elevated liver enzymes (AST and ALT) and alkaline phosphatase, inflammation of the liver (hepatitis) and acute liver injury have been reported uncommonly with the use of duloxetine (affecting up to 1 in 100 people). Hepatic failure and yellowing of the skin and eyes (jaundice) have been reported rarely (up to 1 in 1,000 people) with duloxetine. Most of these side effects occurred during the first months of treatment.	The prescriber should be aware that liver toxicity may occur during treatment. Duloxetine Mylan must not be used in patients with liver disease. Duloxetine Mylan should be used with caution in patients treated with other medicines associated with liver injury.
Suicide attempts and thoughts about committing suicide (Suicidality)	Depression and generalised anxiety disorder are associated with an increased risk of suicidal thoughts, self-harm and suicide, especially in young adults and patients with a history of suicidality. The risk may be increased when first starting antidepressants, and side effects such as suicidal thoughts and	Patients should be closely monitored until an improvement occurs. Improvement may not occur during the first few weeks or more of treatment with Duloxetine Mylan. Patients are advised to tell their doctor if they do not feel better after 4 weeks of treatment. If they have thoughts of harming or killing themselves at any

Risk	What is known	Preventability
	behaviour may occur during treatment or when treatment is discontinued. Suicide attempts and thoughts about committing suicide are uncommon and may affect up to 1 in 100 people given the medicine.	time, they should contact their doctor or go to a hospital straight away. Patients are recommended to tell their relative or a close friend that they are depressed or have an anxiety disorder. It might be helpful to ask a close person for their opinion whether depression or anxiety is getting worse. Patients with a history of suicide-related behaviours should be carefully monitored during treatment.
High blood sugar levels (Hyperglycaemia)	High blood sugar levels may occur in patients while on treatment with duloxetine. High blood sugar levels have been reported as an uncommon side effect (affecting up to 1 in 100 people), mostly in diabetic patients.	Patients should tell their doctor if they have diabetes. Patients and those who care for them should watch for symptoms of high blood sugar levels such as urinating a lot more than usual, drinking a lot more than usual, and feeling weak.
Serious illness with blistering of the skin, mouth, eyes and other parts of the body (Stevens-Johnson syndrome)	Stevens-Johnson syndrome is a life-threatening skin reaction which has been reported rarely with duloxetine (may affect up to 1 in 1,000 people).	Doctors should be aware that Stevens-Johnson syndrome may occur during treatment with Duloxetine Mylan. Doctors should monitor patients for any signs of Stevens-Johnson syndrome.
Bleeding in the stomach and intestine (Gastrointestinal tract bleeding)	Bleeding abnormalities such as gastrointestinal bleeding can occur with medicines known as selective serotonin reuptake inhibitors (SSRIs) and serotonin/noradrenaline reuptake inhibitors (SNRIs) including duloxetine.	Duloxetine Mylan should be used with caution in patients taking other medicines that may increase bleeding such as anticoagulants (blood thinners such as warfarin) and/or medicines known to affect platelet function (such as non-steroidal anti-inflammatory drugs [NSAIDs] such as ibuprofen); caution is also advised in patients with known bleeding tendencies.

Important potential risks

Risk	What is known
Kidney failure (Renal failure)	Kidney problems were very rarely reported in clinical trials and in everyday clinical experience. There was no indication in clinical trials that the risk of kidney failure was higher in duloxetine-treated patients than in placebo-treated patients. However, the prescriber should be aware that

Risk	What is known
	kidney failure may occur during treatment. Patients are advised to inform their doctor before taking duloxetine if they have kidney disease.
Heart and blood vessel problems (cardiovascular events) including heart attack, heart failure and stroke especially when using duloxetine with NSAID	Duloxetine when used together with a medicine called NSAID (such as ibuprofen) has been associated with high blood pressure (hypertension) in some patients. Cases of hypertensive crisis (sudden, dangerously high blood pressure) have been reported rarely with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other heart 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 medicines that may reduce its breakdown in the body. 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. Various heart and blood vessel side effects including disturbed heart function such as a forceful heartbeat that may be rapid or irregular (palpitations) or disturbed heart rhythms (mainly atrial fibrillation), increased heart rate (tachycardia), increase of blood pressure, flushing or fainting (syncope), hypertension, light-headedness or fainting on standing up (orthostatic hypotension) or cold fingers and/or toes (peripheral coldness) may occur. Patients should tell their doctor if they have high blood pressure or heart disease.

Missing information

Risk	What is known
Risk of exposure to duloxetine during pregnancy (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 Mylan should be used in pregnancy only if the potential benefit justifies the potential risk to the unborn child. Women should be advised to notify their physician if they become pregnant, or intend to become pregnant, during therapy.
Use of duloxetine 120 mg in elderly patients	There is limited information regarding the use of duloxetine 120 mg in elderly patients, especially for the treatment of major depressive disorder or generalised anxiety disorder.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Duloxetine Mylan can be found on Duloxetine Mylan's EPAR page.

This medicine has no additional risk minimisation measures.

Planned post-authorisation development plan

No post-authorisation development has been planned as this is a generic medicine.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 05-2015.