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

This is a summary of the risk management plan (RMP) for Duloxetine Zentiva, which details the measures to be taken in order to ensure that Duloxetine Zentiva 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 Zentiva which can be found on Duloxetine Zentiva's EPAR page.

Overview of disease epidemiology

Duloxetine Zentiva is used to treat adults with major depression, pain due to diabetic peripheral neuropathy, or generalised anxiety disorder.

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 Zentiva 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 Zentiva 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 Zentiva 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 has not been studied in children for the treatment of diabetic peripheral neuropathic pain or generalised anxiety disorder. 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 Zentiva while breastfeeding is not recommended.

Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Suicide attempts and thoughts about committing suicide (suicidality)	People with depression and/or anxiety disorders may have thoughts of harming or killing themselves. The risk may be increased when first starting antidepressants 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. Duloxetine Zentiva should not be used in children and adolescents under 18 years. Patients under 18 years of age who take medicines such as duloxetine are at an increased risk of side effects, such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger).	Patients should be closely monitored until an improvement occurs. Improvement may not occur during the first few weeks or more of treatment with Duloxetine Zentiva. 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 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.
Moderate liver disease (hepatic risks)	Liver failure and yellowing of the skin and eyes (jaundice) have been reported rarely (up to 1 in 1,000 people) with duloxetine.	The prescriber should be aware that liver toxicity may occur during treatment. Duloxetine Zentiva must not be used in patients with liver disease

Risk	What is known	Preventability
	Most of these side effects occurred during the first months of treatment. Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported uncommonly with the use of duloxetine (affecting up to 1 in 100 people). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular (damage affecting the liver cells). Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury. Elevations of liver function tests as well as hepatic damage were reported.	resulting in hepatic impairment. Duloxetine Zentiva should be used with caution in patients treated with other medicines associated with liver injury.
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 Zentiva. Doctors should monitor patients for any signs of Stevens-Johnson syndrome.
High blood sugar levels (hyperglycaemia)	High blood sugar levels may occur in patients while on treatment with duloxetine. High blood sugar levels (hyperglycaemia) have been reported with duloxetine treatment 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.
Bleeding in the stomach and intestine (gastrointestinal tract bleeding)	There have been reports of bleeding abnormalities, such as ecchymoses (subcutaneous extravasation of blood,) purpura (red or purple discolorations on the skin that do not blanch on applying pressure) and gastrointestinal haemorrhage with medicines known as selective serotonin reuptake inhibitors and serotonin/noradrenaline reuptake	Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function (such as non-steroidal anti-inflammatory drugs [NSAIDs] such as ibuprofen) and in patients with known bleeding tendencies.

Risk	What is known	Preventability
	inhibitors, including duloxetine.	

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 kidney failure may occur during treatment. Patients are advised to inform their doctor before taking duloxetine if they have kidney disease. No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). Duloxetine Zentiva must not be used in patients with severe renal impairment
Heart and blood vessel problems (cardiovascular events) including heart attack, heart failure and stroke especially when using duloxetine with NSAIDs	Duloxetine when used together with NSAIDs (such as ibuprofen) has been associated with an increase in blood pressure (hypertension). This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis (sudden, dangerously high blood pressure) have been reported 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 is also advised 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
Limited information on use in pregnancy	There are no adequate data on the use of duloxetine in pregnant women. Duloxetine Zentiva should be used in pregnancy only if the potential benefit

Risk	What is known
(prospective data about potential risks of exposure to duloxetine during pregnancy)	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. Studies in animals have shown reproductive toxicity at levels of duloxetine lower than those used in humans. The potential risk for humans is unknown. Duloxetine 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.
Limited information on use of duloxetine 120 mg in elderly patients	No dosage adjustment is recommended for elderly patients solely on the basis of age. However, as with any medicine, caution should be exercised when treating the elderly; especially with duloxetine 120 mg per day for major depressive disorder or generalised anxiety disorder, for which data are limited.

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 Zentiva can be found on Duloxetine Zentiva'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 06-2015.