VI.2 Elements for a Public Summary

DULOXETINE Pharmalex 30 mg hard gastro-resistant capsules
DULOXETINE Pharmalex 60 mg hard gastro-resistant capsules

VI.2.1 Overview of disease epidemiology

Depression (Major depressive disorder)

Major depressive disorder is a mental disorder characterised by a pervasive and persistent low mood that is accompanied by a loss of interest or pleasure in normally enjoyable activities that lasts for more than 2 weeks. It adversely affects a person's family, professional life, sleeping and eating habits, and general health. Aside from a person's personality, social circumstances and physical health factors, disturbances in the serotonin-system in the brain are considered to play a role in the development of depression and related diseases.

Globally, more than 350 million people of all ages suffer from depression. Depression most frequently occurs in patients in their 30s, with a smaller peak when they are in their 50s. More women are affected by depression than men. At its worst, depression can lead to suicide. Suicide results in an estimated 1 million deaths every year.

Treatment options for moderate to severe depression consist of basic psychosocial support combined with antidepressant medication or psychotherapy.

Diabetic peripheral neuropathic pain

Peripheral neuropathy is a term for a group of conditions in which the network of nerves that lie outside the brain and the spinal cord is damaged. Damage to these nerves can cause a wide range of symptoms, such as numbness and tingling in the feet or hands, burning, stabbing or shooting pain in affected areas.

Diabetes (both type 1 and type 2) is the most common cause of peripheral neuropathy. Nerve damage resulting from diabetes can cause pain ('diabetic peripheral neuropathic pain').

Diabetic peripheral neuropathy affects around 110 million people worldwide. It has been estimated to occur in 10 to 100 percent of diabetic patients. It is estimated that approximately 50 percent of patients with diabetes will eventually develop neuropathy.

Treatment for diabetic peripheral neuropathic pain may include painkillers, such as paracetamol and ibuprofen. Medicines used to treat depression (antidepressants), epilepsy or anxiety may be also used for treatment.

Generalised anxiety disorder

Generalized anxiety disorder (GAD) is an anxiety disorder that is characterized by excessive, uncontrollable and often irrational worry which interferes with daily functioning. Physical symptoms, such as headaches, nausea, numbness in hands and feet may also appear.

Risk factors for GAD include overactivity in areas of the brain involved in emotions and behaviour, an imbalance of the brain chemicals serotonin and noradrenaline (involved in the control and regulation of mood), family history, genetic inheritance, having a history of stressful or traumatic experiences, having a painful long-term health condition, having a history of drug or alcohol misuse.

GAD is a common condition, estimated to affect about 1 in every 25 people. Slightly more women are affected than men, and the condition is more common in people between the ages of 35 and 55.

Treatments include various medicines, such as antidepressants or antiepileptics. These may be used in combination with cognitive behavioural therapy.

VI.2.2 Summary of treatment benefits

Major depressive disorder is a mental disorder characterised by a pervasive and persistent low mood accompanied by low self-esteem and loss of interest or pleasure in normally enjoyable activities. Major depressive disorder is a disabling condition that adversely affects the patient's family, work or school life, sleeping and eating habits, and general health.

Diabetic neuropathies are nervous system disorders associated with diabetes mellitus. These conditions are thought to result from injury to small blood vessels that supply nerves in addition to conditions of larger vessels that can culminate in diabetic neuropathy, which manifests itself – besides other symptoms – in pain affecting predominantly legs or feet.

Generalised anxiety disorder is characterized by excessive, uncontrollable and often irrational worry. This excessive worry often interferes with daily functioning. Patients exhibit a variety of physical symptoms, including e.g. fatigue, headaches, numbness in hands and feet, muscle tension, muscle aches, and inability to fully control the anxiety

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor, which means it increases the concentration of both neurotransmitters outside of cells, and therefore enhances the communication between nerve cells.

Pharmacodynamic effects
Duloxetine normalised pain thresholds in several animal models of neuropathic and inflammatory pain and attenuated pain behaviour in a model of persistent pain. The pain inhibitory action of duloxetine is believed to be a result of direct action within the central nervous system.

Clinical efficacy and safety

Major Depressive Disorder: Duloxetine was studied in 3,158 patients with major depression. The efficacy of duloxetine at the recommended dose of 60 mg once a day was demonstrated as measured by improvement in the 17- item Hamilton Depression Rating Scale (a disease-specific questionnaire).

Generalised Anxiety Disorder: Duloxetine demonstrated its efficacy in five studies in patients with generalised anxiety disorder. Efficacy was measured by improvement in the Hamilton Anxiety Scale (HAM-A) total score and by the Sheehan Disability Scale (SDS) global functional impairment score (disease-specific questionnaires).

Diabetic Peripheral Neuropathic Pain: The efficacy of duloxetine as a treatment for diabetic neuropathic pain was established in 2 studies in adults. Efficacy was assessed by the weekly mean of 24-hour average pain, which was collected in a daily diary by patients.

VI.2.3 Unknowns relating to treatment benefits

The safety and efficacy of duloxetine has not sufficiently been studied in paediatric patients.

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.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Risk for the liver (Hepatic risks)	During treatment with DULOXETINE Pharmalex, inflammation of the liver has uncommonly occurred (in up to 1 in 100 people), and liver failure and yellowing of the skin or whites of the eyes (jaundice) has been observed rarely (up to 1 in 1000 people). Additionally, duloxetine may cause effects patients may not be aware of, such as increases in liver enzymes, which can only be noticed during blood tests. Most of these events occurred during the first months of treatment.	DULOXETINE Pharmalex should NOT be taken if a patient has liver disease. The Patient should tell his/her doctor if he/she is currently, has recently been or is planning on taking any other medicines, including medicines obtained without a prescription. Other medicines may be associated with liver damage, and DULOXETINE Pharmalex may not be suitable for every patient. If the patient notices any side effects that could be related to a liver disorder (i.e. abdominal pain, jaundice), he/she should talk to his/her doctor or pharmacist. This medicine should always be taken as prescribed by the doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
Thoughts of harming or killing oneself (Suicidality)	If the patient is depressed and/or has anxiety disorders, thoughts of harming or killing oneself may appear. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer. Patient may be more likely to think like this if he/she has previously had thoughts about killing or harming himself/herself, or if he/she is 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 During treatment with DULOXETINE Pharmalex, suicidal behaviour or suicidal	DULOXETINE Pharmalex should not be used in children and adolescents under 18 years; they have an increased risk of side-effects such as suicide attempt, suicidal thoughts when they take this class of medicines. If a patient has had thoughts of killing or harming himself/herself at any time, he/she should talk to his/her doctor or go to the hospital immediately. A patient should tell a relative or close friend that he/she is taking this medicine and has experienced depression or an anxiety disorder. The patient should ask them to let him/her know if they feel that the depression or anxiety is getting worse or if they notice any changes in behaviour.

	thoughts have rarely occurred (in up to 1 in 1000 people).	
High blood sugar levels (Hyperglycaemia)	Duloxetine may cause effects that patient may not be aware of, such as increases in blood sugar levels, which have uncommonly been observed (in up to 1 in 100 people).	This medicine should always be taken as prescribed by the doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
A severe skin condition characterised by cell death that causes the outer skin layer to separate from deeper layers, and also affecting the mouth, eyes and genitals (Stevens-Johnson Syndrome)	Stevens-Johnson syndrome (serious illness with blistering of the skin, mouth, eyes and genitals) has rarely been observed (in up to 1 in 1000 people)	DULOXETINE Pharmalex should not be taken if the patient is allergic to duloxetine or to any of the other ingredients of this medicine. If, while taking DULOXETINE Pharmalex, blistering on skin, eyes, mouth or genitals is noticed, a doctor should be contacted immediately or the patient should be taken to the hospital; the patient should alwys tell the doctor that he/she is taking DULOXETINE Pharmalex.
Bleeding from the stomach or gut (Gastrointestinal bleeding)	Up to 1 in 100 people taking duloxetine have experienced vomiting blood, black tarry stools (faeces) or gastroenteritis. Passing bright red blood in their stools has occurred rarely (in up to 1 in 1000 people).	The patient should tell his/her doctor before taking DULOXETINE Pharmalex if he/she has a history of bleeding disorders (tendency to develop bruises), or if he/she is taking any medicines which thin the blood or prevent the blood from clotting. These medicines might increase the risk of bleeding. The doctor should be told if the patient is planning on taking any of these medications while taking DULOXETINE Pharmalex. If blood in stools or vomiting blood is noticed, a doctor shuld be contacted immediately or the patient should be taken to the hospital. This medicine should always be taken as prescribed by the doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.

Important potential risks

Risk	**What is known** **(Including reason why it is considered a potential risk)**

Cardiovascular events including those with the concomitant use of NSAIDs (including myocardial infarction, heart failure and stroke)	Patients treated with DULOXETINE Pharmalex may be at an increased risk of developing a heart attack, heart failure or stroke with or without the simultaneous use of a non-steroidal anti-inflammatory drug(s) (e.g. ibuprofen). .
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 Medicines which thin the blood or prevent the blood from clotting, might increase the risk of bleeding.
Renal failure	Patients treated with DULOXETINE Pharmalex may be at an increased risk of developing renal failure. Postmarketing data consistent with renal failure or impairment in temporal association with duloxetine treatment have been reported. However, these data were confounded by medical history, concomitant medications or other disease states, and a causal relationship with duloxetine could not be established.

Missing information

Risk	What is known
Characterisation of the safety and tolerability of duloxetine in paediatric patients	Duloxetine has not been studied in patients under the age of 7. 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.
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. The potential risk for humans is unknown.
Safety of duloxetine in elderly patients ≥ 75 years old with concomitant NSAIDs use	There are no adequate data on the safety of duloxetine with concomitant NSAIDs use in elderly patients ≥ 75 years old.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) 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

No post-authorisation studies have been imposed or are planned.

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

Not applicable