Duloxetin Stada 20 mg gastro-resistant capsules, hard
Duloxetin Stada 40 mg gastro-resistant capsules, hard
Duloxetin Stada 30 mg gastro-resistant capsules, hard
Duloxetin Stada 60 mg gastro-resistant capsules, hard

Version V1.3

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a Public Summary

a. Duloxetin Stada 20 mg gastro-resistant capsules, hard
Duloxetin Stada 40 mg gastro-resistant capsules, hard

b. Duloxetin Stada 30 mg gastro-resistant capsules, hard
Duloxetin Stada 60 mg gastro-resistant capsules, hard

Duloxetin Stada 20 mg gastro-resistant capsules, hard

Duloxetin Stada 40 mg gastro-resistant capsules, hard

VI.2.1a Overview of disease epidemiology

Urinary incontinence is the unintentional passing of urine. Stress urinary incontinence is the most common form of incontinence, where urine leakage occurs upon increased pressure on the bladder, as in coughing, sneezing or exercise. Stress urinary incontinence may develop due to childbirth (especially if multiple vaginal deliveries in the past), obesity or due to bladder damage during surgery or similar. Approximately 4 in 100 adults suffer from urinary incontinence, and well over half of these suffer from stress incontinence. It is estimated that as many as 1 in 5 women over the age of 40 have some degree of stress incontinence. The main treatment for stress incontinence is pelvic floor exercises. Lifestyle changes, bladder training and/or surgery to tighten or support the bladder outlet are other options. Medication may be used in addition to exercises if the patient is not suitable or is not willing to go for a surgery.

VI.2.2a Summary of treatment benefits

Stress urinary incontinence is a medical condition in which patients have accidental loss or leakage of urine during physical exertion or activities such as laughing, coughing, sneezing, lifting, or exercise.

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
In animal studies, increased levels of those two neurotransmitters (5-HT and NA) in the lowest part of the spinal cord led to stimulation of the urethral striated sphincter muscle (the muscle that holds back urine when you laugh, sneeze, or perform physical activities). A similar mechanism in women is believed to result in stronger urethral closure during urine storage with physical stress that could explain the efficacy of duloxetine in the treatment of women with stress urinary incontinence (SUI).

Clinical efficacy and safety
The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four studies with 1913 women (22 to 83 years) with SUI; of these, 958 patients received

duloxetine and 955 received a placebo. Efficacy was measured via diaries, in which Incontinence Episode Frequency (IEF) was recorded, and from incontinence-specific quality of life questionnaire score (I-QOL).

Incontinence Episode Frequency: In all four studies, IEF had decreased by at least half in the duloxetine-treated group compared with just over a third in the placebo-treated group. Differences were observed at each visit after 4 weeks, 8 weeks and 12 weeks of medication.

In an additional study limited to patients with severe SUI, all responses with duloxetine were achieved within 2 weeks.

The efficacy of duloxetine is reinforced when combined with a training program called Pelvic Floor Muscle Training (PFMT).

VI.2.3a Unknowns relating to treatment benefits

The safety and efficacy of duloxetine for the treatment of stress urinary incontinence in children and adolescents younger than 18 years have not been studied. No data are available.
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.2.4a Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Risk for the liver (Hepatic risks)	During treatment with Duloxetin Stada, 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 that you 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.	Do not take Duloxetin Stada if you have liver disease. Tell your doctor or if you are currently, have recently been or are planning on taking any other medicines, including medicines obtained without a prescription. Other medicines may be associated with liver damage, and Duloxetin Stada may not be suitable for you. If you get any side effects that could be related to a liver disorder (i.e. abdominal pain, jaundice), talk to your doctor or pharmacist. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
Thoughts of harming or killing yourself (Suicidality)	Although Duloxetin Stada is not indicated for the treatment of depression, its active ingredient (duloxetine) is used as an antidepressant medicine. If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these	Duloxetin Stada 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 you have thoughts of killing or harming yourself at any time, talk to your doctor or go to a hospital immediately.

	medicines all take time to work, usually about two weeks but sometimes longer. You may be more likely to think like this if you have previously had thoughts about killing or harming yourself, or are 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 Duloxetin Stada, suicidal behaviour or suicidal thoughts have rarely occurred (in up to 1 in 1000 people).	If you are depressed or have an anxiety disorder, tell a relative or close friend that you are taking this medicine, and ask them to let you know if they feel your depression or anxiety is getting worse or if they notice changes in your behaviour.
High blood sugar levels (Hyperglycaemia)	Duloxetine may cause effects that you may not be aware of, such as increases in blood sugar levels, which have uncommonly been observed (in up to 1 in 100 people).	Always take this medicine as prescribed by your 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)	Do not take Duloxetin Stada if you are allergic to duloxetine or any of the other ingredients of this medicine. If, while taking Duloxetin Stada, you notice blistering on your skin, eyes, mouth or genitals, talk to your doctor immediately or go to a hospital; let them know you are taking Duloxetin Stada.
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).	Talk to your doctor before you take Duloxetin Stada if you have a history of bleeding disorders (tendency to develop bruises), or if you are taking any medicines which thin the blood or prevent the blood from clotting. These medicines

		might increase the risk of bleeding. Tell your doctor if you are planning on taking any of these medications while taking Duloxetin Stada. If you notice blood in your stools or if you vomit blood, immediately contact your doctor or go to a hospital. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
Drug reaction caused by high levels of the neurotransmitter serotonin (Serotonin syndrome with concomitant use of MAOIs)	High levels of serotonin can lead to “Serotonin syndrome”,a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles; serotonin syndrome has rarely occurred (in up to 1 in 1000 people) during treatment with Duloxetin Stada.	Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, especially those that increase the level of serotonin. Examples of these are: triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), SNRIs (such as venlafaxine), tricyclic antidepressants (such as clomipramine, amitriptyline), pethidine, St John’s Wort and MAOIs (such as moclobemide and linezolid). If you get any unusual symptom that you think might be serotonin syndrome while taking any of these medicines together with Duloxetin Stada, you should see your doctor.

Important potential risks

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)	Feeling the heart pumping in the chest, fast and/or irregular heart beat has been observed in up to 1 in 100 people.
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. These medicines might increase the risk of bleeding.
Renal failure	Patients treated with Duloxetin Stada 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
Characterization of the safety and tolerability of duloxetine in paediatric patients	The safety and tolerability of duloxetine in paediatric patients in the treatment of stress urinary incontinence has not been studied. No data are available.
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.
Characterization of drug utilization in unapproved indications and populations	Given the fact that duloxetine, albeit at different strengths, is also marketed for additional indications, and given the lack of data precluding its use in children and adolescents, it can not be exluded that the drug is either prescribed for an unapproved indication (e.g. depression, neuropathic pain, anxiety), or taken by non-approved patient populations in their own home.
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.
Long-term safety data in chronic pain patients	There are no adequate data on the safety of duloxetine in chronic pain patients.

VI.2.5a 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.2.6a Planned post authorisation development plan

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

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

Not applicable

Duloxetin Stada 30 mg gastro-resistant capsules, hard

Duloxetin Stada 60 mg gastro-resistant capsules, hard

VI.2.1bOverview 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.2.2bSummary 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.2.3bUnknowns 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.2.4bSummary of safety concerns

Important identified risks

Risk	What is known	Preventability

Risk for the liver (Hepatic risks)	During treatment with Duloxetin Stada, 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 that you 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.	Do not take Duloxetin Stada, if you have liver disease. Tell your doctor or if you are currently, have recently been or are planning on taking any other medicines, including medicines obtained without a prescription. Other medicines may be associated with liver damage, and Duloxetin Stada, may not be suitable for you. If you get any side effects that could be related to a liver disorder (i.e. abdominal pain, jaundice), talk to your doctor or pharmacist. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
Thoughts of harming or killing yourself (Suicidality)	If you are depressed and/or have anxiety disorders you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer. You may be more likely to think like this if you have previously had thoughts about killing or harming yourself, or are 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 Duloxetin Stada, suicidal	Duloxetin Stada, 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 you have thoughts of killing or harming yourself at any time, talk to your doctor or go to a hospital immediately. If you are depressed or have an anxiety disorder, tell a relative or close friend that you are taking this medicine, and ask them to let you know if they feel your depression or anxiety is getting worse or if they notice changes in your behaviour.

	behaviour or suicidal thoughts have rarely occurred (in up to 1 in 1000 people).	
High blood sugar levels (Hyperglycaemia)	Duloxetine may cause effects that you may not be aware of, such as increases in blood sugar levels, which have uncommonly been observed (in up to 1 in 100 people).	Always take this medicine as prescribed by your 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)	Do not take Duloxetin Stada if you are allergic to duloxetine or any of the other ingredients of this medicine. If, while taking Duloxetin Stada, you notice blistering on your skin, eyes, mouth or genitals, talk to your doctor immediately or go to a hospital; let them know you are taking Duloxetin Stada.
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).	Talk to your doctor before you take Duloxetin Stada if you have a history of bleeding disorders (tendency to develop bruises), or if you are taking any medicines which thin the blood or prevent the blood from clotting. These medicines might increase the risk of bleeding. Tell your doctor if you are planning on taking any of these medications while taking Duloxetin Stada. If you notice blood in your stools or if you vomit blood, immediately contact your doctor or go to a hospital. Always take this medicine as prescribed by your doctor and as indicated in the Package Leaflet. This will minimise the risk of developing adverse drug reactions.
Drug reaction caused by high levels of the	High levels of serotonin can lead to “Serotonin	Tell your doctor or pharmacist if you are taking,

neurotransmitter serotonin (Serotonin syndrome)	syndrome",a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles; serotonin syndrome has rarely occurred (in up to 1 in 1000 people) during treatment with Duloxetin Stada.	have recently taken or might take any other medicines, especially those that increase the level of serotonin. Examples of these are: triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), SNRIs (such as venlafaxine), tricyclic antidepressants (such as clomipramine, amitriptyline), pethidine, St John's Wort and MAOIs (such as moclobemide and linezolid). If you get any unusual symptom that you think might be serotonin syndrome while taking any of these medicines together with Duloxetin Stada, you should see your doctor.
High blood pressure (Hypertension)	Duloxetine has been associated with an increase in blood pressure in some patients. Cases of severe increase in blood pressure that can lead to a stroke (hypertensive crisis) have been reported with duloxetine, especially in patients with pre-existing high blood pressure. Duloxetin Stada should therefore not be started in patients with uncontrolled high blood pressure. In patients with known high blood pressure and/or other heart disease, blood pressure monitoring is recommended, especially during the first month of treatment.	Tell your doctor or pharmacist if you have or have ever been diagnosed with hypertension (persistent high blood pressure). Your doctor will monitor your blood pressure regularly and may adapt your dose of Duloxetin Stada or discontinue Duloxetin Stada if your blood pressure persistently too high. Tell your doctor immediately if you experience any of the following: • Severe chest pain • Severe headache, accompanied by confusion and blurred vision • Nausea and vomiting • Severe anxiety • Shortness of breath • Seizures • Unresponsiveness

Important potential risks

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)	Feeling the heart pumping in the chest, fast and/or irregular heart beat has been observed in up to 1 in 100 people.
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. These medicines might increase the risk of bleeding.
Renal failure	Patients treated with Duloxetin Stada 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**
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 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.
Characterization 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.

VI.2.5bSummary 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.2.6bPlanned post authorisation development plan

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

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

Not applicable.