

**APPROVED**  
**by the Order of the Ministry of**  
**Health of Ukraine**  
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**Marketing Authorization**  
**No. UA/18442/01/01**  
**UA/18442/01/02**

**PACKAGE LEAFLET**  
**for medical use of a medicinal product**

Symbiia®

***Qualitative and quantitative composition:***

*active substance:* duloxetine;

1 capsule contains duloxetine hydrochloride 33.7 mg or 67.3 mg, which is equivalent to duloxetine 30 mg or 60 mg;

*list of excipients:* spherical sugar, hydroxypropylcellulose, hypromellose, hypromellose phthalate (HP-55), triethyl citrate, talc;

*capsule shell (for dosage 30 mg):* titanium dioxide (E 171), diamond blue FCF (E 133), hypromellose (E 464), iron oxide black (E 172);

*capsule shell (for dosage 60 mg):* titanium dioxide (E 171), hypromellose (E 464), iron oxide black (E 172);

**Pharmaceutical form.** Intestinal soluble capsules.

*Main physical and chemical properties:*

*capsules 30 mg:* capsules with an opaque gray body and opaque blue cap, marked "DLX 30";

*capsules 60 mg:* capsules with an opaque gray body and opaque blue cap, marked "DLX 60".

**Pharmacotherapeutic group.** Antidepressants. ATC code N06A X21.

***Pharmacological properties.***

*Pharmacodynamic properties.*

Duloxetine is a combined serotonin and norepinephrine reuptake inhibitor. It insignificantly inhibits dopamine uptake, has no significant affinity for histamine and dopamine, cholinergic and adrenergic receptors. The mechanism of action of duloxetine in the treatment of depression is due to inhibition of serotonin and norepinephrine reuptake and, as a result, increased serotonergic and noradrenergic neurotransmission in the central nervous system. Duloxetine also has an analgesic effect, which is probably the result of slowing the transmission of pain impulses in the central nervous system.

*Pharmacokinetic properties.*

*Absorption.* With oral administration, duloxetine is well absorbed. The maximum blood plasma concentration is achieved 6 hours after medicinal product administration. Food delays the absorption time, the time to reach the maximum concentration increases from 6 to 10 hours, while absorption decreases (approximately 11 %).

*Distribution.* Duloxetine is efficiently bound to blood plasma proteins (approximately 96 %) with both albumin and  $\alpha_1$ -acid glycoprotein. Hepatic or renal failure do not affect the binding of proteins.

*Metabolism.* Duloxetine is metabolized with the participation of CYP2D6 and CYP1A2 isoenzymes. The metabolites formed are not pharmacologically active.

*Excretion.* The half-life of duloxetine is 12 hours. The average clearance of duloxetine in blood plasma is 101 l/h.

*Renal failure.* In patients with the terminal stage of renal failure, which are constantly on dialysis, there was a double increase in the concentration of duloxetine and the values of the area under the pharmacokinetic concentration-time curve (AUC) compared to healthy volunteers. Therefore, a lower initial dose should be used for patients with chronic renal failure. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

#### Hepatic impairment

Moderate liver disease (Child-Pugh classification class B) affected the pharmacokinetic properties of duloxetine. Compared to healthy volunteers, the apparent plasma clearance of duloxetine was 79% lower, the apparent half-life was 2.3-fold longer, and the AUC was 3.7-fold higher in patients with moderate liver disease. The pharmacokinetics of duloxetine and its metabolites have not been studied in patients with mild or severe hepatic impairment.

### **Clinical particulars.**

#### ***Therapeutic indications.***

Treatment of major depressive disorder.

Treatment of diabetic peripheral neuropathic pain.

Treatment of generalized anxiety disorder.

#### ***Contraindications.***

Contraindication for the use of the medicinal product is hypersensitivity to duloxetine or to any of the excipients of the medicinal product.

Duloxetine cannot be co-administered with non-selective irreversible monoamine oxidase inhibitors (MAOIs) or for at least 14 days after discontinuation of MAOIs. Due to the period of half-life of duloxetine, the MAO inhibitors cannot be prescribed for at least 5 days after discontinuation of duloxetine.

Symbiia® cannot be prescribed to patients with unstable hypertension, as this can provoke a hypertensive crisis.

The medicinal product cannot be prescribed to patients with terminal stage of renal disease (creatinine clearance - up to 30 ml/min).

Symbiia® should not be prescribed to patients with liver disease as it can cause hepatic failure.

Duloxetine is not recommended to be prescribed to children due to a lack of data on its safety and the effectiveness of the use of this age category of patients.

Symbiia® should not be used in combination with fluvoxamine, ciprofloxacin or enoxacin (strong CYP1A2 inhibitors) due to increased blood plasma concentrations of duloxetine.

#### ***Interaction with other medicinal products and other forms of interaction.***

*Medicinal products metabolized by CYP1A2.* During the clinical study, in the case of the co-administration of theophylline, a CYP1A2 substrate, with a duloxetine (60 mg twice daily) their pharmacokinetics did not significantly affect each other.

*CYP1A2 inhibitors.* Due to CYP1A2 is involved in the metabolism of duloxetine, co-administration of duloxetine with potent CYP1A2 inhibitors will probably lead to an increase of the duloxetine concentrations. Fluvoxamine (100 mg once daily), which is a potent inhibitor of CYP1A2, reduces duloxetine plasma clearance by approximately 77 % and increases AUC<sub>0-t</sub> by 6-fold. Therefore, Symbiia® cannot be co-administered with CYP1A2 inhibitors, in particular with fluvoxamine.

*Medicinal products metabolized by CYP2D6.* Duloxetine is a moderate CYP2D6 inhibitor. When the duloxetine is administered at a dose of 60 mg twice daily with a single dose of desipramine, which is a substrate of CYP2D6, the AUC of desipramine is increased 3 times. Co-administration of duloxetine (40 mg twice daily) increases the steady-state AUC of tolterodine (2 mg twice daily) by 71%, but does not affect the pharmacokinetic properties of 5-hydroxyl metabolite, so no dosage adjustments are recommended. It is recommended to use the Symbiia® with caution in combination with medicinal products that are mainly metabolized by CYP2D6 (risperidone, tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline and imipramine), especially if they have a narrow therapeutic index (e.g., flecainide, propafenone and metoprolol).

*Medicinal products acting on the central nervous system.* When the duloxetine is prescribed in combination with other medicinal products and substances that act on the central nervous system, especially with a similar mechanism of action, including alcohol and sedative medicinal products (e.g., benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines) must be taken precautions.

*MAO inhibitors.* Duloxetine should not be co-administered with non-selective irreversible MAO inhibitors due to the risk of the occurrence of serotonin syndrome. When taking reversible selective MAO inhibitors, such as moclobemide, the risk of serotonin syndrome is lower, but the use of such a combination is not recommended. The antibiotic linezolid is a reversible non-selective MAO inhibitor and should not be used in patients receiving Symbiia® (see section “Special warnings and precautions for use”).

*Serotonin syndrome.* Caution should be exercised when prescribing Symbiia® in combination with serotonergic and tricyclic antidepressants, such as clomipramine or amitriptyline, together with moclobemide or linezolid, St. John's wort (*Hypericum perforatum*) or triptans, tramadol, peptidine, tryptophan.

*Oral contraceptives and other steroid agents.* The results of *in vitro* studies show that duloxetine does not stimulate the catalytic activity of CYP3A. No specific *in vivo* medicinal product interaction studies have been performed.

*Anticoagulants and antithrombotic agents.* Duloxetine should be used with caution in combination with oral anticoagulants and antithrombotic agents due to an increased risk of bleeding due to pharmacodynamic interactions. In addition, an increase in INR was observed when duloxetine was administered to patients receiving warfarin. However, concomitant use of duloxetine and warfarin in stationary conditions in healthy volunteers as part of the study of clinical pharmacology did not result in a clinically significant change in baseline INR or in the pharmacokinetic properties of R- or S-warfarin.

*Medicinal products containing duloxetine.* Concomitant use with other medicinal products containing duloxetine should be avoided.

*Medicinal products containing St. John's wort.* When used together, adverse reactions often occur.

*Antacids and H<sub>2</sub> antagonists.* Concomitant use of duloxetine with antacids containing aluminum and magnesium, or duloxetine with famotidine, did not affect the rate or degree of absorption of duloxetine after administration of an oral dose of 40 mg.

*CYP1A2 inducers.* Population pharmacokinetic analysis showed that smokers had almost 50% lower than the concentration of duloxetine in the blood plasma compared to persons who do not smoke.

### ***Special warnings and precautions for use.***

#### **WARNING**

Patients with a high risk of suicide during treatment should be closely monitored, as the possibility of suicide attempt is not excluded before the onset of significant remission.

The possibility of using duloxetine hydrochloride has not been studied in patients under 18 years of age, so it is not intended for use in this age group.

*Epileptic seizures and mania.* As in the case of the use of other medicinal products acting on the central nervous system, duloxetine should be used as a precaution in patients with a history of seizures, mania, or bipolar disorder.

*Mydriasis.* There were reports of the mydriasis associated with duloxetine, therefore caution should be exercised when prescribing duloxetine to patients with high intraocular pressure or acute narrow-angle glaucoma.

*Blood pressure and heart rate.* In some patients, the administration of duloxetine leads to an increase in blood pressure and clinically significant arterial hypertension. Blood pressure monitoring is recommended in patients with hypertension and/or other heart diseases. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis with duloxetine have been reported, especially in patients with hypertension. Therefore, it is recommended to monitor blood pressure in patients with known hypertension and/or other heart disease, especially during the first month of treatment. Symbiia® should be used with caution in patients whose condition may be at risk due to

increased heart rate or high blood pressure. Duloxetine should also be used with caution with medicinal products that may impair its metabolism (see section "Interaction with other medicinal products and other forms of interaction"). For patients who have a persistent increase in blood pressure while taking Symbiia®, it is necessary to resolve the issue of a reduction in the dose or gradual cessation of the use of the medicinal product (see section "Undesirable effect"). Symbiia® should not be used in patients with uncontrolled arterial hypertension (see section "Contraindications").

*Renal failure.* The increased concentration of duloxetine in the blood plasma is observed in patients with severe renal impairment during hemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section "Contraindications". For information on patients with mild or moderate renal dysfunction, see section "Posology and method of administration".

*Hemorrhages.* Bleeding disorders such as bruising, in particular purpura, gastrointestinal bleeding, with selective serotonin reuptake inhibitors (SSRIs) and selective serotonin and norepinephrine reuptake inhibitors (SSNRIs), including duloxetine, have been reported. Caution is advised in patients taking anticoagulants and/or medicinal products that may affect platelet function (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid) and in patients with a known tendency to bleed.

*Serotonin syndrome.* As in the case of other serotonergic agents, serotonin syndrome may become potentially life-threatening with duloxetine treatment, especially with concomitant use of other serotonergic agents (including SSRIs, SSNRIs, tricyclic antidepressants, or triptans), agents that worsen serotonin metabolism, such as MAO, or with antipsychotics or other dopamine antagonists that may affect serotonergic neurotransmitter systems (see sections "Contraindications" and "Interaction with other medicinal products and other forms of interaction").

Symptoms of serotonin syndrome may include changes in mental status (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoherence), and/or symptoms of gastrointestinal tract (e.g., nausea, vomiting, diarrhea).

If concomitant treatment with duloxetine and other serotonergic agents that can affect the serotonergic and/or dopaminergic neurotransmitter systems is clinically warranted, close monitoring of the patient is recommended, especially when initiating treatment and increasing the dose.

*Hyponatremia.* Cases of hyponatremia, including serum sodium levels below 110 mmol/L, have been reported with duloxetine. Hyponatremia can be caused by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Most cases of hyponatremia have been reported in the elderly, especially in combination with the conditions that lead to a change in the balance of the fluid. Is necessary with caution to prescribe patients with an increased risk of hyponatremia (e.g. elderly patients), patients with cirrhosis of the liver, dehydrated patients and patients receiving diuretics.

*Medicinal products containing St. John's wort.* Adverse reactions can be more common with the simultaneous use of the medicinal product Symbiia® and medicinal products containing the herb St. John's wort (*Hypericum perforatum*).

*Withdrawal syndrome.* Withdrawal symptoms often occur, especially with a sudden cessation of treatment. The risk of withdrawal symptoms when using SSRIs and SSNRIs depends on several factors, including the duration and dose of therapy and the rate of dose reduction. The most commonly described reactions are listed in the section "Undesirable effects". These symptoms are usually mild or moderate, but in some patients they can be severe in patients, usually occurring during the first few days after the cessation of treatment. Very rarely, such symptoms have been observed in patients who accidentally missed the dose. These symptoms are independently reduced and usually disappear within 2 weeks, although in some people they can be long-lasting (2-3 months or more). Therefore, it is recommended to gradually reduce the dose of duloxetine upon discontinuation of treatment for at least 2 weeks according to the patient's needs (see section "Posology and method of administration").

*Akathisia/psychomotor anxiety.* Manifestations of akathisia (characterized by subjectively unpleasant or anxious anxiety and the need to move, often accompanied by the inability to sit or stand still) occur during the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be harmful.

*Increased levels of liver enzymes.* Cases of hepatic impairment have been reported with duloxetine,

including severe elevations in liver enzymes (> 10-fold upper limit of the normal), hepatitis, and jaundice (see section “Undesirable effects”). Most often, these phenomena were reported during the first months of treatment. The liver damage most often has a hepatocellular character. Duloxetine should be used with caution in patients taking medicinal products that can cause liver damage.

*Sexual dysfunction.* SSRIs/SSNRIs can cause symptoms of sexual dysfunction (see section “Undesirable effects”). Long-term sexual dysfunction has been reported when the symptoms persisted despite discontinuation of SSRIs/SSNRIs.

*Suicide.*

*Major depressive disorder and generalized anxiety disorder.* Depression is associated with an increased risk of suicidal ideation, self-harm and suicide (suicide-related phenomena). The risk exists until significant remission is achieved. The patient's condition must be closely monitored until a significant improvement is achieved, as remission cannot occur for the first few weeks or more of treatment. It is known from general clinical experience that the risk of suicide increases in the initial stages of treatment.

Other mental states for which Symbiia® is prescribed are also associated with an increased risk of suicide phenomena. In addition, these mental states can be comorbid if they are accompanied by major depressive disorder. Therefore, it is necessary to take precautions in the treatment of patients with major depressive disorder and other mental conditions. Patients with a history of suicidal phenomena or a significant level of suicidal ideation are at increased risk of suicidal behavior and should be monitored more closely during treatment. Cases of suicidal ideation and suicidal behavior have been reported during or immediately after duloxetine therapy. During therapy, especially in the early stages, it is necessary to carefully monitor patients, first of all, those that are in the risk group, as well as to carry out the corresponding change in the dosage. Patients and caregivers should be informed about the need to control any clinical deterioration, suicidal behavior or thoughts and unusual behavioral changes and immediately consult a doctor when they occur.

*Diabetic peripheral neuropathic pain.* Isolated cases of suicidal ideation and suicidal behaviors have been reported during or immediately after duloxetine therapy, as well as when administered other medicinal products with similar pharmacological action (antidepressants). Doctors must inform patients about the need to report any feeling of concern.

*Elderly patients.* Data on the use of the medicinal product Symbiia® in a dosage of 120 mg in the elderly patients with major depressive disorder and generalized anxiety disorder is limited. Therefore, caution should be taken when using the medicinal product in elderly patients with the maximum dosage (see section "Posology and method of administration").

*Serious skin reactions.* The following skin reactions have been reported very rarely in post-marketing studies: angioneurotic edema, contusion, hemorrhage, Stevens-Johnson syndrome, bruising, urticaria.

*Medicinal products containing duloxetine.* Duloxetine is used under different trademarks for several indications (diabetic neuropathic pain, major depressive disorder, generalized anxiety disorder and stress urinary incontinence). The use of several of these medicinal products at the same time should be avoided.

*The presence of sucrose.* Symbiia® intestinal soluble capsules should not be prescribed to patients with hereditary fructose intolerance, malabsorption syndrome, sucrase-isomaltase insufficiency.

*Fertility, pregnancy and lactation.*

#### Fertility

In animal studies, duloxetine did not affect male fertility, and the effects in women were seen only at doses that caused maternal toxicity.

#### Pregnancy

Adequate and controlled studies of the actions of the medicinal product in pregnant women have not been carried out, so its use during pregnancy is not recommended. There is no adequate data from the use of duloxetine in pregnant women. Animal studies have shown that reproductive toxicity with systemic exposure (AUC) of duloxetine is lower than the maximum clinical effect. The potential risk for humans is unknown. Epidemiological data indicate that the use of SSRIs during pregnancy, especially in late pregnancy, can increase the risk of persistent pulmonary hypertension in newborn

(PPHN). Although the association of PPHN with the treatment of SSNRIs has not been studied, this potential risk cannot be excluded using duloxetine, taking into account the relevant mechanism of action (inhibition of serotonin reuptake reception). As with the administration of other serotonergic medicinal products, in infants can be observed withdrawal symptoms if the mother has used duloxetine before childbirth. Symptoms of withdrawal syndrome include orthostatic hypotension, tremor, increased neuro-reflex excitability syndrome, difficulty swallowing, sucking, respiratory disorders, epileptic seizures. In most cases, these symptoms were observed immediately after birth or during the first few days of life. It is necessary to recommend to women to inform the doctor that they become pregnant or going to get pregnant during administration of duloxetine.

The use of the medicinal product during pregnancy is recommended only if the expected effect exceeds the risk.

#### Lactation

Duloxetine is poorly excreted into breast milk. The approximate dose received by the child (at the rate of 1 mg per 1 kg of body weight) is 0.14% of the maternal dose. The safety of the use of duloxetine in children is unknown, so breast-feeding while taking duloxetine is not recommended.

#### *Effects on ability to drive and use machines.*

The study of the effect of duloxetine on ability to drive and use machines or operating machinery have not been performed. The medicinal product may have a sedative effect and dizziness. During treatment, it is necessary to refrain from driving and potentially dangerous activities that require increased attention and speed of psychomotor reactions.

#### ***Posology and method of administration.***

*Major depressive disorder.* The initial and recommended maintenance dose is 60 mg 1 time per day, used regardless of food intake. Dosage more than 60 mg 1 time per day to the maximum 120 mg per day were estimated in terms of safety. However, there is no clinical data on the fact that increasing the dose will be effective for patients who do not respond to the initial recommended dose.

The therapeutic response is usually observed after 2-4 weeks of treatment.

After a persistent antidepressant effect, it is recommended to continue treatment for several months to avoid recurrence. In patients who respond to duloxetine and have a history of recurrent episodes of major depression, further long-term treatment at a dose 60-120 mg per day should be considered.

*Diabetic peripheral neuropathic pain.* The recommended initial dose is 60 mg 1 time per day, used regardless of food intake. Some patients can be prescribed a daily dose above 60 mg up to a maximum dose of 120 mg per day, divided into 2 doses.

The therapeutic treatment effect is manifested within 2 months. In patients with an inadequate initial response, an additional response after this period is unlikely. Therapeutic benefits should be evaluated regularly (at least every 3 months).

*Generalized anxiety disorder.* The recommended initial dose is 30 mg 1 time per day, used regardless of food intake. In case of insufficient effect of the treatment, the dose should be increased to 60 mg per day. In case of insufficient effect of treatment in a dose of 60 mg it is possible to consider an increase in a dose to 90 or 120 mg per day.

The therapeutic effect of treatment is manifested within 2-4 weeks. Once the response has been established, it is recommended to continue treatment for several months to avoid recurrence.

*Patients with renal impairment.* No dose adjustment is required for patients with mild to moderate renal impairment (creatinine clearance 30-80 ml/min). Symbiia® is not used to treat patients with terminal stage renal disease (creatinine clearance <30 ml/min).

*Patients with hepatic impairment.* The medicinal product cannot be prescribed to patients with liver disease or liver failure.

*Elderly patients.* For elderly patients, it is not recommended to adjust doses based on age. As with any medicinal products, caution should be taken in the treatment of elderly patients, especially when using Symbiia® at a dose of 120 mg per day for major depressive disorder or generalized anxiety disorder.

*Treatment cessation.* Sudden cessation of treatment should be avoided. The dose must be gradually reduced for a period of at least one to two weeks to reduce the risk of withdrawal reactions. If intolerable symptoms occur after dose reduction or after discontinuation of treatment, the medicinal product can be resumed at the previously set dose. Over time, the doctor may continue to reduce the dose, but more gradually.

#### *Children.*

Clinical studies on the use of duloxetine in children (under 18 years of age) have not been performed, so it is not used in pediatric practice.

#### **Overdose.**

Clinical data on duloxetine overdose is limited. Cases of an overdose with duloxetine at a dose of 5 400 mg as monotherapy or in combination with other medicinal products have been reported. Fatalities have been reported, primarily with mixed overdose, as well as using duloxetine at a dose of approximately 1000 mg.

*Symptoms.* Symptoms of overdose (mainly during combination with other medicinal products) included drowsiness, coma, serotonin syndrome, convulsions, epileptic seizures, vomiting, and tachycardia.

*Treatment of overdose.* Specific antidotes are unknown, with the appearance of serotonin syndrome, specific treatment is necessary (ciprogeptadine and/or temperature control). Patency of airways must be checked. It is recommended to monitor cardiac activity and control basic vital signs together with appropriate symptomatic and supportive measures. Gastric lavage can be appropriate if it is carried out immediately after taking the medicinal product or in patients with existing symptoms of overdose. Activated charcoal reduces the absorption of the medicinal product. Duloxetine has a large volume of distribution in the body, therefore forced diuresis, hemoperfusion and metabolic perfusion are unlikely to be useful.

#### **Undesirable effects.**

Dizziness, nausea, and headache (> 5%) have been reported as adverse symptoms upon discontinuation of duloxetine. Sensitivity disorders, sleep disorders, agitation or anxiety, tremor, irritability, diarrhea and hyperhidrosis have also been observed with discontinuation of the medicinal product. The table shows adverse reactions when taking duloxetine according to data obtained from spontaneous reports and in placebo-controlled clinical studies.

Adverse events have been ranked under headings of frequency using the following convention: very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1000$ ,  $< 1/100$ ); rare ( $\geq 1/10000$ ,  $< 1/1000$ ); very rare ( $< 1/10000$ ).

Very common	Common	Uncommon	Rare	Very rare
<i>Eye disorders:</i>				
	Blurry image	Mydriasis, visual impairment, eye dryness	Glaucoma	
<i>Ear and labyrinth disorders</i>				
	Tinnitus <sup>1</sup>	Dizziness, ear pain		
<i>Respiratory, thoracic and mediastinal disorders</i>				
	Oscitation, oropharyngeal pain	Feeling of tightness in the throat, nosebleeds		
<i>Gastrointestinal disorders</i>				
Nausea (24.3 %), dry mouth (12.8 %)	Constipation, diarrhea, vomiting, dyspepsia, meteorism, abdominal pain	Gastrointestinal bleeding <sup>7</sup> , gastroenteritis, belching, gastritis	Stomatitis, bad breath, the presence of blood in the stool, microscopic colitis	

<i>Hepatobiliary disorders</i>				
		Elevated levels of liver enzymes (ALT, AST, basic phosphatase), hepatitis <sup>3</sup> , acute liver damage	Jaundice <sup>6</sup> , hepatic failure <sup>6</sup>	
<i>Renal and urinary disorders</i>				
	Dysuria	Urinary retention, difficulty starting to urinate, nocturia, polyuria, decreased urine flow	Abnormal smell of urine	
<i>Endocrine disorders</i>				
			Hypothyroidism;	
<i>Metabolic and nutritional disorders</i>				
	Decreased appetite.	Hyperglycemia (especially in patients with diabetes)	Dehydration, hyponatremia, SISADH	
<i>Nervous system disorders</i>				
Headache (14.3 %), drowsiness (10.7 %), dizziness (0.2 %)	Tremor, paresthesia	Myoclonus, akathisia <sup>7</sup> , nervousness, attention disorders, lethargy, dyskinesia, taste disorders, restless legs syndrome, poor sleep	Serotonin syndrome <sup>6</sup> , convulsions <sup>1</sup> , psychomotor anxiety <sup>6</sup> , extrapyramidal disorders <sup>6</sup>	
<i>Psychiatric disorders</i>				
	Insomnia, agitation, decreased libido, anxiety, abnormal visions and abnormal orgasm	Sleep disorders, bruxism, disorientation, apathy, suicidal thinking <sup>5,7</sup>	Mania, hallucinations, aggression and malice <sup>4</sup> , suicidal behavior <sup>5,7</sup>	
<i>Cardiac disorders</i>				
	Feeling of palpitations, hot flashes	Tachycardia, supraventricular arrhythmia, fibrillation, often atrial. Hypertension <sup>3,7</sup> , increase in arterial pressure <sup>3</sup> , orthostatic hypotension <sup>3</sup> , faintness <sup>2</sup> , feeling of cold in extremities	Hypertensive crisis <sup>3,6</sup>	
<i>Immune system disorders</i>				
			Anaphylactic reactions, hypersensitivity	
<i>Skin and subcutaneous tissue disorders</i>				
	Increased sweating, rash	Night sweats, contact dermatitis, urticaria, cold sweats,	Angioneurotic edema <sup>6</sup> , Stevens-Johnson syndrome <sup>6</sup>	Cutaneous vasculitis

		photosensitization, increased tendency to form bruises		
<i>Musculoskeletal and connective tissue disorders:</i>				
	Musculoskeletal pain, muscle spasm	Muscle twitching, a feeling of muscle tightness	Trismus	
<i>Reproductive system and breast disorders</i>				
	Erectile dysfunction, violation or delay of ejaculation	Menstrual disorders, sexual disorders, gynecological bleeding	Symptoms of menopause, galactorrhea, hyperprolactinemia	
<i>General disorders and administration site conditions</i>				
	Fatigue	Chest pain <sup>7</sup> ; fall <sup>8</sup> ; feeling unwell, feeling cold, feeling "creeping sensation", thirst, malaise, feeling hot, gait disturbance		
<i>Infections and invasions</i>				
		Laryngitis		
<i>Investigations:</i>				
	Body weight loss	Body weight gain, increased creatine phosphokinase	Increased blood cholesterol	

- <sup>1</sup> Cases of seizures and ringing in the ears were observed after interruption of treatment.
- <sup>2</sup> Cases of orthostatic hypotension and loss of consciousness were observed mainly at the beginning of treatment.
- <sup>3</sup> Patients who have a persistent increase in blood pressure when taking duloxetine should reduce the dose or gradually discontinue medicinal product therapy.
- <sup>4</sup> Cases of aggression and anger were reported at the beginning of treatment and after interruption of treatment.
- <sup>5</sup> Cases of suicidal thinking and behavior have been reported at the beginning of treatment and immediately after treatment discontinuation.
- <sup>6</sup> The established frequency of adverse reactions from post-marketing studies was not observed in placebo-controlled clinical studies.
- <sup>7</sup> They did not differ statistically significantly from placebo.
- <sup>8</sup> Cases of falls were more common in the elderly patients ( $\geq 65$  years).

Termination of therapy (especially a sudden interruption) is often accompanied by withdrawal syndrome. The most common side effects in this case are dizziness, drowsiness, sensory disorders (including paresthesia), sleep disorders (including insomnia and severe delirium), weakness, anxiety or aggression, nausea and/or vomiting, tremor, headache, irritability, diarrhea, hyperhidrosis and vertigo. Gradual discontinuation of therapy is recommended. These events are usually mild or moderate and self-monitoring for SSRIs and SSNRIs, but in some patients they can be severe and/or prolonged. Therefore, gradual discontinuation of dose reduction is recommended if duloxetine treatment is no longer required (see sections "Special warnings and precautions for use" and "Posology and method of administration").

In a 12-week acute phase of duloxetine studies in patients with diabetic neuropathic pain, small, but statistically significant increase in blood glucose levels in an empty stomach in patients with duloxetine were observed. The HbA1c was stable in both duloxetine and placebo patients. In the follow-up phase of these studies, which lasted up to 52 weeks, there was an increase in HbA1c levels in both the duloxetine group and in the group of ordinary care, but the average increase in the

duloxetine treatment group was 0.3 %. An insignificant increase in the level of glucose in the blood of an empty stomach and the total cholesterol in patients receiving duloxetine was also observed, while in these laboratory studies there was a slight decrease in the number of risk groups.

The QT interval with heart rate correction in patients taking duloxetine did not differ from patients taking placebo. No clinically significant differences in QT, PR, QRS, or QTcB measurements were observed between patients taking duloxetine and placebo.

*Renal failure.*

Patients with severe renal insufficiency (creatinine clearance <30 ml/min) on hemodialysis have increased plasma levels of duloxetine.

*Hepatitis/increases of hepatic enzyme levels.*

Cases of liver damage have been reported, including significant elevations in liver enzymes (up to 10-fold higher than normal), hepatitis, and jaundice. Most of these events occurred during the first month of treatment. The most common variant of liver damage is hepatocellular. Duloxetine should be used with caution in patients taking medicinal products that can cause liver damage.

A slight increase in blood potassium levels has been reported. Transient abnormal potassium levels were uncommon in duloxetine-treated patients compared with placebo.

Reported suspected adverse reactions.

Reporting suspected adverse reactions after registration of a medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective drug. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

***Shelf life*** 2 years.

**Special precautions for storage.**

Store in the original package at a temperature not exceeding 25 ° C.

Keep out of the reach of children.

**Nature and contents of container.**

7 capsules in a blister, 4 blister in a carton pack.

**Category of release.**

Prescription only medicine.

**Marketing authorisation holder.** PrJSC “Pharmaceutical firm “Darnitsa”.

**The marketing authorisation holder 's location and address of the place of business.**

13, Boryspilska Street, Kyiv, 02093, Ukraine.

**Manufacturer.** Balkanpharma-Dupnica JSC.

**The manufacturer's location and address of the place of business.**

3 Samokovsko Shosse, Dupnitsa 2600, Bulgaria.

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