

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 40 mg hard gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 40 mg of duloxetine (as hydrochloride).

Excipient(s) with known effect:

Each capsule may contain up to 74 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

Opaque orange body, imprinted with '40mg' and an opaque blue cap, imprinted with '9545'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

YENTREVE is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI).

YENTREVE is indicated in adults.

For further information see section 5.1.

4.2 Posology and method of administration

Posology

The recommended dose of YENTREVE is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.

A 20 mg capsule is also available. However, limited data are available to support the efficacy of YENTREVE 20 mg twice daily.

The efficacy of YENTREVE has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining YENTREVE with a pelvic floor muscle training (PFMT) programme may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

Hepatic impairment

YENTREVE must not be used in women with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

Renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). YENTREVE must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

Paediatric population

The safety and efficacy of duloxetine for the treatment of stress urinary incontinence has not been studied. No data are available.

Special populations

Elderly

Caution should be exercised when treating the elderly.

Discontinuation of treatment

Abrupt discontinuation should be avoided. When stopping treatment with YENTREVE the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Liver disease resulting in hepatic impairment (see section 5.2).

YENTREVE should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors - MAOIs (see section 4.5).

YENTREVE should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacin since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with YENTREVE is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and seizures

YENTREVE should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs tricyclic antidepressants or triptans), with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular

aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If concomitant treatment with duloxetine and other serotonergic agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems in clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

St John's wort

Adverse reactions may be more common during concomitant use of YENTREVE and herbal preparations containing St John's wort (*Hypericum perforatum*).

Mydriasis

Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate

Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac 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 medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

Haemorrhage

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.

Discontinuation of treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial, adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with YENTREVE and 24% of patients taking placebo.

The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Hyponatraemia

Hyponatraemia has been reported when administering YENTREVE, including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics.

Depression, suicidal ideation and behaviour

Although YENTREVE is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medicinal product. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on YENTREVE therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of YENTREVE is recommended (see section 4.2).

Use in children and adolescents under 18 years of age

YENTREVE should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (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 compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Medicinal products containing duloxetine

Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive disorder, generalised anxiety disorder and stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes

Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Akathisia/psychomotor restlessness

The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Sucrose

YENTREVE hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine should not be used in combination with non-selective irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping YENTREVE before starting an MAOI (see section 4.3).

The concomitant use of YENTREVE with selective, reversible MAOIs, like moclobemide, is not recommended (see section 4.4). The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with YENTREVE (see section 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of YENTREVE with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC_{0-t} 6-fold. Therefore YENTREVE should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

CNS medicinal products: Caution is advised when YENTREVE is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Serotonergic agents: In rare cases, serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic agents. Caution is advisable if YENTREVE is used concomitantly with serotonergic agents like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, MOAIs like moclobemide or linezolid, St John's wort (*Hypericum perforatum*) or triptans, tramadol, pethidine and tryptophan (see section 4.4).

Effect of duloxetine on other medicinal products

Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

Medicinal products metabolised by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if YENTREVE is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Oral contraceptives and other steroidal agents: Results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction. Furthermore, increases in INR values have been reported when duloxetine was co-administered to patients treated with warfarin. However, concomitant

administration of duloxetine with warfarin under steady state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of R- or S-warfarin.

Effects of other medicinal products on duloxetine

Antacids and H₂ antagonists: Co-administration of YENTREVE with aluminium- and magnesium-containing antacids or with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Inducers of CYP1A2: Population pharmacokinetic studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Fertility, pregnancy and lactation

Fertility

Duloxetine had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

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 (see section 5.3).

The potential risk for humans is unknown.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with duloxetine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

YENTREVE 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.

Breast feeding

Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of YENTREVE while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. YENTREVE may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse events in patients treated with YENTREVE in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouth fatigue and constipation. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

b. Tabulated summary of adverse reactions

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials.

Table 1: Adverse reactions

Frequency estimate: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare
<i>Infections and infestations</i>				
		Laryngitis		
<i>Immune system disorders</i>				
		Hyper-sensitivity disorder	Anaphylactic reaction	
<i>Endocrine disorders</i>				
		Hypo-thyroidism		
<i>Metabolism and nutrition disorders</i>				
	Appetite decreased	Dehydration	Hyperglycaemia (reported especially in diabetic patients) Hyponatraemia SIADH ⁶	
<i>Psychiatric disorders</i>				
	Insomnia Agitation Libido decreased Anxiety Sleep disorder	Bruxism Disorientation Apathy Orgasm abnormal Abnormal dreams	Suicidal behaviour ^{5,6} Suicidal ideation ^{5,7} Mania ⁶ Hallucinations Aggression and anger ^{4,6}	
<i>Nervous system disorders</i>				
	Headache Dizziness Lethargy Somnolence Tremor Paraesthesia	Nervousness Disturbance in attention Dysgeusia Poor quality sleep	Serotonin syndrome ⁶ Convulsions ^{1,6} Myoclonus Akathisia ⁶ Psychomotor restlessness ⁶ Extra-pyramidal symptoms ⁶ Dyskinesia Restless legs	

Very common	Common	Uncommon	Rare	Very Rare
			syndrome	
<i>Eye disorders</i>				
	Blurred vision	Mydriasis Visual impairment Dry eye	Glaucoma	
<i>Ear and labyrinth disorders</i>				
	Vertigo	Tinnitus ¹ Ear pain		
<i>Cardiac disorders</i>				
		Palpitations Tachycardia	Supra-ventricular arrhythmia, mainly atrial fibrillation ⁶	
<i>Vascular disorders</i>				
	Hypertension ^{3,7} Flushing	Syncope ² Blood pressure increase ³	Hypertensive crisis ³ Orthostatic hypotension ² Peripheral coldness	
<i>Respiratory, thoracic and mediastinal disorders</i>				
		Yawning	Throat tightness Epistaxis	
<i>Gastrointestinal disorders</i>				
Nausea Dry mouth Constipation	Diarrhoea Abdominal pain Vomiting Dyspepsia	Gastrointestinal haemorrhage ⁷ Gastroenteritis Stomatitis Eructation Gastritis Dysphagia Flatulence Breath odour	Haematochezia Microscopic colitis ⁹	
<i>Hepato-biliary disorders</i>				
		Hepatitis ³ Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury	Hepatic failure ⁶ Jaundice ⁶	
<i>Skin and subcutaneous tissue disorders</i>				
	Sweating increased	Rash Night sweats Urticaria Dermatitis contact Cold sweat Increased tendency to bruise	Stevens-Johnson Syndrome ⁶ Angio-neurotic oedema ⁶ Photo-sensitivity reactions	Cutaneous vasculitis
<i>Musculoskeletal and connective tissue disorders</i>				
		Musculo-skeletal pain Muscle tightness Muscle spasm Trismus	Muscle twitching	

Very common	Common	Uncommon	Rare	Very Rare
<i>Renal and urinary disorders</i>				
		Urinary hesitation Dysuria Nocturia Pollakiuria Urine odour abnormal	Urinary retention ⁶ Polyuria Urine flow decreased	
<i>Reproductive system and breast disorders</i>				
		Gynaecological haemorrhage Menopausal symptoms	Menstrual disorder Galactorrhoea Hyperprolactinaemia	
<i>General disorders and administration site conditions</i>				
Fatigue	Asthenia Chills	Chest pain ⁷ Falls ⁸ Feeling abnormal Feeling cold Thirst Malaise Feeling hot	Gait disturbance	
<i>Investigations</i>				
		Weight decrease Weight increase Blood cholesterol increased Blood creatine phosphokinase increased	Blood potassium increased	

¹ Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.

² Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

³ See section 4.4.

⁴ Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.

⁵ Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4).

⁶ Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.

⁷ Not statistically significantly different from placebo.

⁸ Falls were more common in the elderly (≥ 65 years old).

⁹ Estimated frequency based on all clinical trial data.

c. Description of selected adverse reactions

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhidrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA_{1c} was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

4.9 Overdose

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for duloxetine but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Mechanism of action

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

Pharmacodynamic effects

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. 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 SUI.

Clinical efficacy and safety

The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies that randomised 1913 women (22 to 83 years) with SUI; of

these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

Incontinence Episode Frequency: In all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed at each visit after 4 weeks (duloxetine 54% and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

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

The efficacy of YENTREVE has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of YENTREVE compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, YENTREVE may provide no benefit beyond that afforded by more conservative behavioural interventions.

Quality of Life: Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement, $p < 0.001$). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%, $p < 0.001$).

YENTREVE and Prior Continence Surgery: There are limited data that suggest that the benefits of YENTREVE are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

YENTREVE and Pelvic Floor Muscle Training (PFMT): During a 12-week blinded, randomised, controlled study, YENTREVE demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than YENTREVE alone or PFMT alone.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Yentreve in all subsets of the paediatric population in the treatment of stress urinary incontinence. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Absorption: Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance.

Distribution: Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites

glucuronide conjugate of 4-hydroxy duloxetine and sulfate conjugate of 5-hydroxy 6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

Elimination: The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special populations

Gender: Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age: Pharmacokinetic differences have been identified between younger and elderly females (≥ 65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C_{max} and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment: Moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times 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 insufficiency.

Breast-feeding mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 $\mu\text{g/day}$ while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats. Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown. Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposure levels below maximum clinical exposure (AUC).

Studies in juvenile rats reveal transient effects on neurobehaviour, as well as significantly decreased body weight and food consumption; hepatic enzyme induction; and hepatocellular vacuolation at 45 mg/kg/day. The general toxicity profile of duloxetine in juvenile rats was similar to that in adult rats. The no-adverse effect level was determined to be 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Hypromellose
Hypromellose acetate succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate

Capsule shell:

Gelatin
Sodium lauryl sulfate
Titanium dioxide (E171)
Indigo carmine (E132)
Red iron oxide (E172)
Yellow iron oxide (E172)
Edible black ink

Edible ink:

Black iron oxide - synthetic (E172)
Propylene glycol
Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30° C.

6.5 Nature and contents of container

Polyvinylchloride (PVC), polyethylene (PE), and polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminium foil.

Packs of 28, 56, 98, 140 and 196 (2x98) capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/280/002

EU/1/04/280/003

EU/1/04/280/004

EU/1/04/280/005

EU/1/04/280/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 August 2004

Date of latest renewal: 24 June 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 20 mg hard gastro-resistant capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 20 mg of duloxetine (as hydrochloride).

Excipient(s) with known effect:

Each capsule may contain up to 37 mg sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard gastro-resistant capsule.

Opaque blue body, imprinted with '20 mg' and an opaque blue cap, imprinted with '9544'.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

YENTREVE is indicated for women for the treatment of moderate to severe Stress Urinary Incontinence (SUI).

YENTREVE is indicated in adults.

For further information see section 5.1.

4.2 Posology and method of administration

Posology

The recommended dose of YENTREVE is 40 mg twice daily without regard to meals. After 2-4 weeks of treatment, patients should be re-assessed in order to evaluate the benefit and tolerability of the therapy. Some patients may benefit from starting treatment at a dose of 20 mg twice daily for two weeks before increasing to the recommended dose of 40 mg twice daily. Dose escalation may decrease, though not eliminate, the risk of nausea and dizziness.

However, limited data are available to support the efficacy of YENTREVE 20 mg twice daily.

The efficacy of YENTREVE has not been evaluated for longer than 3 months in placebo-controlled studies. The benefit of treatment should be re-assessed at regular intervals.

Combining YENTREVE with a pelvic floor muscle training (PFMT) programme may be more effective than either treatment alone. It is recommended that consideration be given to concomitant PFMT.

Hepatic impairment

YENTREVE must not be used in women with liver disease resulting in hepatic impairment (see sections 4.3 and 5.2).

Renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal dysfunction (creatinine clearance 30 to 80 ml/min). YENTREVE must not be used in patients with severe renal impairment (creatinine clearance <30 ml/min; see section 4.3).

Paediatric population

The safety and efficacy of duloxetine for the treatment of stress urinary incontinence has not been studied. No data are available.

Special populations

Elderly

Caution should be exercised when treating the elderly.

Discontinuation of treatment

Abrupt discontinuation should be avoided. When stopping treatment with YENTREVE the dose should be gradually reduced over a period of at least one to two weeks in order to reduce the risk of withdrawal reactions (see sections 4.4 and 4.8). If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate.

Method of administration

For oral use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Liver disease resulting in hepatic impairment (see section 5.2).

YENTREVE should not be used in combination with nonselective, irreversible monoamine oxidase inhibitors - MAOIs (see section 4.5).

YENTREVE should not be used in combination with CYP1A2 inhibitors, like fluvoxamine, ciprofloxacin or enoxacin since the combination results in elevated plasma concentrations of duloxetine (see section 4.5).

Severe renal impairment (creatinine clearance <30 ml/min) (see section 4.4).

The initiation of treatment with YENTREVE is contraindicated in patients with uncontrolled hypertension that could expose patients to a potential risk of hypertensive crisis (see sections 4.4 and 4.8).

4.4 Special warnings and precautions for use

Mania and seizures

YENTREVE should be used with caution in patients with a history of mania or a diagnosis of bipolar disorder, and/or seizures.

Serotonin syndrome

As with other serotonergic agents, serotonin syndrome, a potentially life-threatening condition, may occur with duloxetine treatment, particularly with concomitant use of other serotonergic agents (including SSRIs, SNRIs tricyclic antidepressants or triptans), with agents that impair metabolism of serotonin such as MAOIs, or with antipsychotics or other dopamine antagonists that may affect the serotonergic neurotransmitter systems (see sections 4.3 and 4.5).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea).

If concomitant treatment with duloxetine and other serotonergic agents that may affect the serotonergic and/or dopaminergic neurotransmitter systems in clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

St John's wort

Adverse reactions may be more common during concomitant use of YENTREVE and herbal preparations containing St John's wort (*Hypericum perforatum*).

Mydriasis

Mydriasis has been reported in association with duloxetine, therefore, caution should be used when prescribing duloxetine in patients with increased intraocular pressure, or those at risk of acute narrow-angle glaucoma.

Blood pressure and heart rate

Duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients. This may be due to the noradrenergic effect of duloxetine. Cases of hypertensive crisis have been reported with duloxetine, especially in patients with pre-existing hypertension. Therefore, in patients with known hypertension and/or other cardiac 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 medicinal products that may impair its metabolism (see section 4.5). For patients who experience a sustained increase in blood pressure while receiving duloxetine either dose reduction or gradual discontinuation should be considered (see section 4.8). In patients with uncontrolled hypertension duloxetine should not be initiated (see section 4.3).

Renal impairment

Increased plasma concentrations of duloxetine occur in patients with severe renal impairment on haemodialysis (creatinine clearance <30 ml/min). For patients with severe renal impairment, see section 4.3. See section 4.2 for information on patients with mild or moderate renal dysfunction.

Haemorrhage

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.

Discontinuation of treatment

Withdrawal symptoms when treatment is discontinued are common, particularly if discontinuation is abrupt (see section 4.8). In a clinical trial, adverse events seen on abrupt treatment discontinuation occurred in approximately 44% of patients treated with YENTREVE and 24% of patients taking placebo.

The risk of withdrawal symptoms seen with SSRI's and SNRI's may be dependent on several factors including the duration and dose of therapy and the rate of dose reduction. The most commonly reported reactions are listed in section 4.8. Generally these symptoms are mild to moderate, however, in some patients they may be severe in intensity. They usually occur within the first few days of discontinuing treatment, but there have been very rare reports of such symptoms in patients who have inadvertently missed a dose. Generally these symptoms are self-limiting and usually resolve within 2 weeks, though in some individuals they may be prolonged (2-3 months or more). It is therefore advised that duloxetine should be gradually tapered when discontinuing treatment over a period of no less than 2 weeks, according to the patient's needs (see section 4.2).

Hyponatraemia

Hyponatraemia has been reported when administering YENTREVE, including cases with serum sodium lower than 110 mmol/l. Hyponatraemia may be due to a syndrome of inappropriate anti-diuretic hormone secretion (SIADH). The majority of cases of hyponatraemia were reported in the elderly, especially when coupled with a recent history of, or condition pre-disposing to, altered fluid balance. Caution is required in patients at increased risk for hyponatraemia, such as elderly, cirrhotic, or dehydrated patients or patients treated with diuretics.

Depression, suicidal ideation and behaviour

Although YENTREVE is not indicated for the treatment of depression, its active ingredient (duloxetine) also exists as an antidepressant medicinal product. Depression is associated with an increased risk of suicidal thoughts, self harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Patients with a history of suicide-related events or those exhibiting a significant degree of suicidal thoughts prior to commencement of treatment are known to be at a greater risk of suicidal thoughts or suicidal behaviour, and should receive careful monitoring during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant medicinal products in psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Cases of suicidal thoughts and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.8). Physicians should encourage patients to report any distressing thoughts or feelings or depressive symptoms at any time. If while on YENTREVE therapy, the patient develops agitation or depressive symptoms, specialised medical advice should be sought, as depression is a serious medical condition. If a decision to initiate antidepressant pharmacological therapy is taken, the gradual discontinuation of YENTREVE is recommended (see section 4.2).

Use in children and adolescents under 18 years of age

YENTREVE should not be used in the treatment of children and adolescents under the age of 18 years. Suicide-related behaviours (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 compared to those treated with placebo. If, based on clinical need, a decision to treat is nevertheless taken, the patient should be carefully monitored for the appearance of suicidal symptoms. In addition, long-term safety data in children and adolescents concerning growth, maturation and cognitive and behavioural development are lacking.

Medicinal products containing duloxetine

Duloxetine is used under different trademarks in several indications (treatment of diabetic neuropathic pain, major depressive disorder, generalised anxiety disorder and stress urinary incontinence). The use of more than one of these products concomitantly should be avoided.

Hepatitis/increased liver enzymes

Cases of liver injury, including severe elevations of liver enzymes (>10 times upper limit of normal), hepatitis and jaundice have been reported with duloxetine (see section 4.8). Most of them occurred during the first months of treatment. The pattern of liver damage was predominantly hepatocellular. Duloxetine should be used with caution in patients treated with other medicinal products associated with hepatic injury.

Akathisia/psychomotor restlessness

The use of duloxetine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Sucrose

YENTREVE hard gastro-resistant capsules contain sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrose-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Monoamine oxidase inhibitors (MAOIs): Due to the risk of serotonin syndrome, duloxetine should not be used in combination with non-selective irreversible monoamine oxidase inhibitors (MAOIs), or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping YENTREVE before starting an MAOI (see section 4.3).

The concomitant use of YENTREVE with selective, reversible MAOIs, like moclobemide, is not recommended (see section 4.4). The antibiotic linezolid is a reversible non-selective MAOI and should not be given to patients treated with YENTREVE (see section 4.4).

Inhibitors of CYP1A2: Because CYP1A2 is involved in duloxetine metabolism, concomitant use of YENTREVE with potent inhibitors of CYP1A2 is likely to result in higher concentrations of duloxetine. Fluvoxamine (100 mg once daily), a potent inhibitor of CYP1A2, decreased the apparent plasma clearance of duloxetine by about 77% and increased AUC_{0-t} 6-fold. Therefore YENTREVE should not be administered in combination with potent inhibitors of CYP1A2 like fluvoxamine (see section 4.3).

CNS medicinal products: Caution is advised when YENTREVE is taken in combination with other centrally acting medicinal products or substances, including alcohol and sedative medicinal products (e.g. benzodiazepines, morphinomimetics, antipsychotics, phenobarbital, sedative antihistamines).

Serotonergic agents: In rare cases, serotonin syndrome has been reported in patients using SSRIs/SNRIs concomitantly with serotonergic agents. Caution is advisable if YENTREVE is used concomitantly with serotonergic agents like SSRIs, SNRIs, tricyclic antidepressants like clomipramine or amitriptyline, MAOIs like moclobemide or linezolid, St John's wort (*Hypericum perforatum*) or triptans, tramadol, pethidine and tryptophan (see section 4.4).

Effect of duloxetine on other medicinal products

Medicinal products metabolised by CYP1A2: The pharmacokinetics of theophylline, a CYP1A2 substrate, were not significantly affected by co-administration with duloxetine (60 mg twice daily).

Medicinal products metabolised by CYP2D6: Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered at a dose of 60 mg twice daily with a single dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. The co-administration of duloxetine (40 mg twice daily) increases steady state AUC of tolterodine (2 mg twice daily) by 71 %, but does not affect the pharmacokinetics of its active 5-hydroxyl metabolite and no dosage adjustment is recommended. Caution is advised if YENTREVE is co-administered with medicinal products that are predominantly metabolised by CYP2D6 (risperidone, tricyclic antidepressants [TCAs] such as nortriptyline, amitriptyline, and imipramine) particularly if they have a narrow therapeutic index (such as flecainide, propafenone and metoprolol).

Oral contraceptives and other steroidal agents: Results of *in vitro* studies demonstrate that duloxetine does not induce the catalytic activity of CYP3A. Specific *in vivo* drug interaction studies have not been performed.

Anticoagulants and antiplatelet agents: Caution should be exercised when duloxetine is combined with oral anticoagulants or antiplatelet agents due to a potential increased risk of bleeding attributable to a pharmacodynamic interaction. Furthermore, increases in INR values have been reported when duloxetine was co-administered to patients treated with warfarin. However, concomitant administration of duloxetine with warfarin under steady state conditions, in healthy volunteers, as part of a clinical pharmacology study, did not result in a clinically significant change in INR from baseline or in the pharmacokinetics of R- or S-warfarin.

Effects of other medicinal products on duloxetine

Antacids and H₂ antagonists: Co-administration of YENTREVE with aluminium- and magnesium-containing antacids or with famotidine had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose.

Inducers of CYP1A2: Population pharmacokinetic studies analyses have shown that smokers have almost 50% lower plasma concentrations of duloxetine compared with non-smokers.

4.6 Fertility, pregnancy and lactation

Fertility

Duloxetine had no effect on male fertility, and effects in females were only evident at doses that caused maternal toxicity.

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 (see section 5.3).

The potential risk for humans is unknown.

Epidemiological data have suggested that the use of SSRIs in pregnancy, particularly in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). Although no studies have investigated the association of PPHN to SNRI treatment, this potential risk cannot be ruled out with duloxetine taking into account the related mechanism of action (inhibition of the re-uptake of serotonin).

As with other serotonergic medicinal products, discontinuation symptoms may occur in the neonate after maternal duloxetine use near term. Discontinuation symptoms seen with duloxetine may include hypotonia, tremor, jitteriness, feeding difficulty, respiratory distress and seizures. The majority of cases have occurred either at birth or within a few days of birth.

YENTREVE 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.

Breast feeding

Duloxetine is very weakly excreted into human milk based on a study of 6 lactating patients, who did not breast feed their children. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose (see section 5.2). As the safety of duloxetine in infants is not known, the use of YENTREVE while breast-feeding is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. YENTREVE may be associated with sedation and dizziness. Patients should be instructed that if they experience sedation or dizziness they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse events in patients treated with YENTREVE in clinical trials in SUI and other lower urinary tract disorders were nausea, dry mouth fatigue and constipation. The data analysis of four 12-week, placebo-controlled clinical trials in patients with SUI, including 958 duloxetine-treated and 955 placebo-treated patients, showed that the onset of the reported adverse events typically occurred in the first week of therapy. However, the majority of the most frequent adverse events were mild to moderate and resolved within 30 days of occurrence (e.g. nausea).

b. Tabulated summary of adverse reactions

Table 1 gives the adverse reactions observed from spontaneous reporting and in placebo-controlled clinical trials.

Table 1: Adverse reactions

Frequency estimate: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common	Common	Uncommon	Rare	Very Rare
<i>Infections and infestations</i>				
		Laryngitis		
<i>Immune system disorders</i>				
		Hyper-sensitivity disorder	Anaphylactic reaction	
<i>Endocrine disorders</i>				
		Hypo-thyroidism		
<i>Metabolism and nutrition disorders</i>				
	Appetite decreased	Dehydration	Hyperglycaemia (reported especially in diabetic patients) Hyponatraemia SIADH ⁶	
<i>Psychiatric disorders</i>				
	Insomnia Agitation Libido decreased Anxiety Sleep disorder	Bruxism Disorientation Apathy Orgasm abnormal Abnormal dreams	Suicidal behaviour ^{5,6} Suicidal ideation ^{5,7} Mania ⁶ Hallucinations Aggression and anger ^{4,6}	

Very common	Common	Uncommon	Rare	Very Rare
<i>Nervous system disorders</i>				
	Headache Dizziness Lethargy Somnolence Tremor Paraesthesia	Nervousness Disturbance in attention Dysgeusia Poor quality sleep	Serotonin syndrome ⁶ Convulsions ^{1,6} Myoclonus Akathisia ⁶ Psychomotor restlessness ⁶ Extra-pyramidal symptoms ⁶ Dyskinesia Restless legs syndrome	
<i>Eye disorders</i>				
	Blurred vision	Mydriasis Visual impairment Dry eye	Glaucoma	
<i>Ear and labyrinth disorders</i>				
	Vertigo	Tinnitus ¹ Ear pain		
<i>Cardiac disorders</i>				
		Palpitations Tachycardia	Supra-ventricular arrhythmia, mainly atrial fibrillation ⁶	
<i>Vascular disorders</i>				
	Hypertension ^{3,7} Flushing	Syncope ² Blood pressure increase ³	Hypertensive crisis ³ Orthostatic hypotension ² Peripheral coldness	
<i>Respiratory, thoracic and mediastinal disorders</i>				
		Yawning	Throat tightness Epistaxis	
<i>Gastrointestinal disorders</i>				
Nausea Dry mouth Constipation	Diarrhoea Abdominal pain Vomiting Dyspepsia	Gastrointestinal haemorrhage ⁷ Gastroenteritis Stomatitis Eructation Gastritis Dysphagia Flatulence Breath odour	Haematochezia Microscopic colitis ⁹	
<i>Hepato-biliary disorders</i>				
		Hepatitis ³ Elevated liver enzymes (ALT, AST, alkaline phosphatase) Acute liver injury	Hepatic failure ⁶ Jaundice ⁶	

Very common	Common	Uncommon	Rare	Very Rare
<i>Skin and subcutaneous tissue disorders</i>				
	Sweating increased	Rash Night sweats Urticaria Dermatitis contact Cold sweat Increased tendency to bruise	Stevens-Johnson Syndrome ⁶ Angio-neurotic oedema ⁶ Photo-sensitivity reactions	Cutaneous vasculitis
<i>Musculoskeletal and connective tissue disorders</i>				
		Musculo-skeletal pain Muscle tightness Muscle spasm Trismus	Muscle twitching	
<i>Renal and urinary disorders</i>				
		Urinary hesitation Dysuria Nocturia Pollakiuria Urine odour abnormal	Urinary retention ⁶ Polyuria Urine flow decreased	
<i>Reproductive system and breast disorders</i>				
		Gynaecological haemorrhage Menopausal symptoms	Menstrual disorder Galactorrhoea Hyperprolactinaemia	
<i>General disorders and administration site conditions</i>				
Fatigue	Asthenia Chills	Chest pain ⁷ Falls ⁸ Feeling abnormal Feeling cold Thirst Malaise Feeling hot	Gait disturbance	
<i>Investigations</i>				
		Weight decrease Weight increase Blood cholesterol increased Blood creatine phosphokinase increased	Blood potassium increased	

¹ Cases of convulsion and cases of tinnitus have also been reported after treatment discontinuation.

² Cases of orthostatic hypotension and syncope have been reported especially at the initiation of treatment.

³ See section 4.4.

⁴ Cases of aggression and anger have been reported particularly early in treatment or after treatment discontinuation.

⁵ Cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation (see section 4.4).

⁶ Estimated frequency of post-marketing surveillance reported adverse reactions; not observed in placebo-controlled clinical trials.

⁷ Not statistically significantly different from placebo.

⁸ Falls were more common in the elderly (≥ 65 years old).

⁹ Estimated frequency based on all clinical trial data.

c. Description of selected adverse reactions

Discontinuation of duloxetine (particularly when abrupt) commonly leads to withdrawal symptoms. Dizziness, sensory disturbances (including paraesthesia or electric shock-like sensations, particularly in the head), sleep disturbances (including insomnia and intense dreams), fatigue, somnolence, agitation or anxiety, nausea and/or vomiting, tremor, headache, myalgia, irritability, diarrhoea, hyperhydrosis and vertigo are the most commonly reported reactions.

Generally, for SSRIs and SNRIs, these events are mild to moderate and self-limiting, however, in some patients they may be severe and/or prolonged. It is therefore advised that when duloxetine treatment is no longer required, gradual discontinuation by dose tapering should be carried out (see sections 4.2 and 4.4).

The heart rate-corrected QT interval in duloxetine-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, QRS, or QTcB measurements between duloxetine-treated and placebo-treated patients.

In the 12 week acute phase of three clinical trials of duloxetine in patients with diabetic neuropathic pain, small but statistically significant increases in fasting blood glucose were observed in duloxetine-treated patients. HbA_{1c} was stable in both duloxetine-treated and placebo-treated patients. In the extension phase of these studies, which lasted up to 52 weeks, there was an increase in HbA_{1c} in both the duloxetine and routine care groups, but the mean increase was 0.3% greater in the duloxetine-treated group. There was also a small increase in fasting blood glucose and in total cholesterol in duloxetine-treated patients while those laboratory tests showed a slight decrease in the routine care group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#)

4.9 Overdose

Cases of overdoses, alone or in combination with other medicinal products, with duloxetine doses of 5400 mg were reported. Some fatalities have occurred, primarily with mixed overdoses, but also with duloxetine alone at a dose of approximately 1000 mg. Signs and symptoms of overdose (duloxetine alone or in combination with other medicinal products) included somnolence, coma, serotonin syndrome, seizures, vomiting and tachycardia.

No specific antidote is known for duloxetine but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. A free airway should be established. Monitoring of cardiac and vital signs is recommended, along with appropriate symptomatic and supportive measures. Gastric lavage may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal may be useful in limiting absorption. Duloxetine has a large volume of distribution and forced diuresis, haemoperfusion, and exchange perfusion are unlikely to be beneficial.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antidepressants. ATC code: N06AX21.

Mechanism of action

Duloxetine is a combined serotonin (5-HT) and noradrenaline (NA) reuptake inhibitor. It weakly inhibits dopamine reuptake with no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors.

Pharmacodynamic effects

In animal studies, increased levels of 5-HT and NE in the sacral spinal cord, lead to increased urethral tone via enhanced pudendal nerve stimulation to the urethral striated sphincter muscle only during the storage phase of the micturition cycle. 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 SUI.

Clinical efficacy and safety

The efficacy of duloxetine 40 mg given twice daily in the treatment of SUI was established in four double-blind, placebo-controlled studies that randomised 1913 women (22 to 83 years) with SUI; of these, 958 patients were randomised to duloxetine and 955 to placebo. The primary efficacy measures were Incontinence Episode Frequency (IEF) from diaries and an incontinence specific quality of life questionnaire score (I-QOL).

Incontinence Episode Frequency: In all four studies the duloxetine-treated group had a 50% or greater median decrease in IEF compared with 33% in the placebo-treated group. Differences were observed at each visit after 4 weeks (duloxetine 54% and placebo 22%), 8 weeks (52% and 29%), and 12 weeks (52% and 33%) of medication.

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

The efficacy of YENTREVE has not been evaluated for longer than 3 months in placebo-controlled studies. The clinical benefit of YENTREVE compared with placebo has not been demonstrated in women with mild SUI, defined in randomised trials as those with IEF < 14 per week. In these women, YENTREVE may provide no benefit beyond that afforded by more conservative behavioural interventions.

Quality of Life: Incontinence Quality of Life (I-QOL) questionnaire scores were significantly improved in the duloxetine-treated patient group compared with the placebo-treated group (9.2 versus 5.9 score improvement, $p < 0.001$). Using a global improvement scale (PGI), significantly more women using duloxetine considered their symptoms of stress incontinence to be improved with treatment compared with women using placebo (64.6% versus 50.1%, $p < 0.001$).

YENTREVE and Prior Continence Surgery: There are limited data that suggest that the benefits of YENTREVE are not diminished in women with stress urinary incontinence who have previously undergone continence surgery.

YENTREVE and Pelvic Floor Muscle Training (PFMT): During a 12-week blinded, randomised, controlled study, YENTREVE demonstrated greater reductions in IEF compared with either placebo treatment or with PFMT alone. Combined therapy (duloxetine + PFMT) showed greater improvement in both pad use and condition-specific quality of life measures than YENTREVE alone or PFMT alone.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Yentreve in all subsets of the paediatric population in the treatment of stress urinary incontinence. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Duloxetine is administered as a single enantiomer. Duloxetine is extensively metabolised by oxidative

enzymes (CYP1A2 and the polymorphic CYP2D6), followed by conjugation. The pharmacokinetics of duloxetine demonstrate large intersubject variability (generally 50-60%), partly due to gender, age, smoking status and CYP2D6 metaboliser status.

Absorption: Duloxetine is well absorbed after oral administration with a C_{max} occurring 6 hours post dose. The absolute oral bioavailability of duloxetine ranged from 32% to 80% (mean of 50%). Food delays the time to reach the peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (approximately 11 %). These changes do not have any clinical significance.

Distribution: Duloxetine is approximately 96% bound to human plasma proteins. Duloxetine binds to both albumin and alpha-1 acid glycoprotein. Protein binding is not affected by renal or hepatic impairment.

Biotransformation: Duloxetine is extensively metabolised and the metabolites are excreted principally in urine. Both cytochromes P450-2D6 and 1A2 catalyse the formation of the two major metabolites glucuronide conjugate of 4-hydroxy duloxetine and sulfate conjugate of 5-hydroxy 6-methoxy duloxetine. Based upon *in vitro* studies, the circulating metabolites of duloxetine are considered pharmacologically inactive. The pharmacokinetics of duloxetine in patients who are poor metabolisers with respect to CYP2D6 has not been specifically investigated. Limited data suggest that the plasma levels of duloxetine are higher in these patients.

Elimination: The elimination half-life of duloxetine ranges from 8 to 17 hours (mean of 12 hours). After an intravenous dose the plasma clearance of duloxetine ranges from 22 l/hr to 46 l/hr (mean of 36 l/hr). After an oral dose the apparent plasma clearance of duloxetine ranges from 33 to 261 l/hr (mean 101 l/hr).

Special populations

Gender: Pharmacokinetic differences have been identified between males and females (apparent plasma clearance is approximately 50% lower in females). Based upon the overlap in the range of clearance, gender-based pharmacokinetic differences do not justify the recommendation for using a lower dose for female patients.

Age: Pharmacokinetic differences have been identified between younger and elderly females (≥ 65 years) (AUC increases by about 25% and half-life is about 25% longer in the elderly), although the magnitude of these changes is not sufficient to justify adjustments to the dose. As a general recommendation, caution should be exercised when treating the elderly (see sections 4.2 and 4.4).

Renal impairment: End stage renal disease (ESRD) patients receiving dialysis had 2-fold higher duloxetine C_{max} and AUC values compared with healthy subjects. Pharmacokinetic data on duloxetine is limited in patients with mild or moderate renal impairment.

Hepatic impairment: Moderate liver disease (Child Pugh Class B) affected the pharmacokinetics of duloxetine. Compared with healthy subjects, the apparent plasma clearance of duloxetine was 79% lower, the apparent terminal half-life was 2.3 times longer, and the AUC was 3.7 times 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 insufficiency.

Breast-feeding mothers: The disposition of duloxetine was studied in 6 lactating women who were at least 12-weeks postpartum. Duloxetine is detected in breast milk, and steady-state concentrations in breast milk are about one-fourth those in plasma. The amount of duloxetine in breast milk is approximately 7 $\mu\text{g/day}$ while on 40 mg twice daily dosing. Lactation did not influence duloxetine pharmacokinetics.

5.3 Preclinical safety data

Duloxetine was not genotoxic in a standard battery of tests and was not carcinogenic in rats.

Multinucleated cells were seen in the liver in the absence of other histopathological changes in the rat carcinogenicity study. The underlying mechanism and the clinical relevance are unknown.

Female mice receiving duloxetine for 2 years had an increased incidence of hepatocellular adenomas and carcinomas at the high dose only (144 mg/kg/day), but these were considered to be secondary to hepatic microsomal enzyme induction. The relevance of this mouse data to humans is unknown. Female rats receiving duloxetine before and during mating and early pregnancy had a decrease in maternal food consumption and body weight, oestrous cycle disruption, decreased live birth indices and progeny survival, and progeny growth retardation at systemic exposure levels estimated to be at the most at maximum clinical exposure (AUC). In an embryotoxicity study in the rabbit, a higher incidence of cardiovascular and skeletal malformations was observed at systemic exposure levels below the maximum clinical exposure (AUC). No malformations were observed in another study testing a higher dose of a different salt of duloxetine. In pre/postnatal toxicity study in the rat, duloxetine induced adverse behavioural effects in the offspring at systemic exposure levels below maximum clinical exposure (AUC).

Studies in juvenile rats reveal transient effects on neurobehaviour, as well as significantly decreased body weight and food consumption; hepatic enzyme induction; and hepatocellular vacuolation at 45 mg/kg/day. The general toxicity profile of duloxetine in juvenile rats was similar to that in adult rats. The no-adverse effect level was determined to be 20 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Hypromellose
Hypromellose acetate succinate
Sucrose
Sugar spheres
Talc
Titanium dioxide (E171)
Triethyl citrate

Capsule shell:

Gelatin
Sodium lauryl sulfate
Titanium dioxide (E171)
Indigo carmine (E132)
Edible black ink

Edible ink:

Black iron oxide - synthetic (E172)
Propylene glycol
Shellac

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture. Do not store above 30° C.

6.5 Nature and contents of container

Polyvinylchloride (PVC), polyethylene (PE), and polychlorotrifluoroethylene (PCTFE) blister sealed with an aluminium foil.

Packs of 28, 56 and 98 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/280/001

EU/1/04/280/007

EU/1/04/280/008

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 August 2004

Date of latest renewal: 24 June 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Lilly S.A.
Avda. de la Industria N° 30,
28108 Alcobendas
Madrid
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 40 MG HARD GASTRO-RESISTANT CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 40 mg hard gastro-resistant capsules.
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg of duloxetine (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains sucrose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 hard gastro-resistant capsules
56 hard gastro-resistant capsules
98 hard gastro-resistant capsules
140 hard gastro-resistant capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/280/002 (28 hard gastro-resistant capsules)
EU/1/04/280/003 (56 hard gastro-resistant capsules)
EU/1/04/280/004 (98 hard gastro-resistant capsules)
EU/1/04/280/005 (140 hard gastro-resistant capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

YENTREVE 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 98 CAPSULES (40 MG) AS INTERMEDIATE PACK / COMPONENT OF A MULTIPACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 40 mg hard gastro-resistant capsules.
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg of duloxetine (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains sucrose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

98 capsules
Component of a multipack comprising 2 packs, each containing 98 capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30 °C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/280/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

YENTREVE 40 mg

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER WRAPPER LABEL ON MULTIPACKS (2X98 CAPSULES, 40 MG) WRAPPED IN
FOIL (INCLUDING BLUE BOX)**

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 40 mg hard gastro-resistant capsules.
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 40 mg of duloxetine (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains sucrose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Multipack comprising 2 packs, each containing 98 capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS
OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF
APPROPRIATE**

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/280/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

YENTREVE 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS (40 mg hard gastro-resistant capsules)

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 40 mg hard gastro-resistant capsules
Duloxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTONS FOR 20 MG HARD GASTRO-RESISTANT CAPSULES

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 20 mg hard gastro-resistant capsules.
Duloxetine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each capsule contains 20 mg of duloxetine (as hydrochloride)

3. LIST OF EXCIPIENTS

Contains sucrose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

56 hard gastro-resistant capsules
28 hard gastro-resistant capsules
98 hard gastro-resistant capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture. Do not store above 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/280/001 (56 hard gastro-resistant capsules)

EU/1/04/280/007 (28 hard gastro-resistant capsules)

EU/1/04/280/008 (98 hard gastro-resistant capsules)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

YENTREVE 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS (20 mg hard gastro-resistant capsules)

1. NAME OF THE MEDICINAL PRODUCT

YENTREVE 20 mg hard gastro-resistant capsules
Duloxetine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Lilly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

YENTREVE 40 mg hard gastro-resistant capsules

YENTREVE 20 mg hard gastro-resistant capsules

Duloxetine (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any of the side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

1. What YENTREVE is and what it is used for
2. What you need to know before you take YENTREVE
3. How to take YENTREVE
4. Possible side effects
5. How to store YENTREVE
6. Contents of the pack and other information

1. What YENTREVE is and what it is used for

YENTREVE contains the active substance duloxetine. YENTREVE increases the levels of serotonin and noradrenaline in the nervous system.

YENTREVE is a medicine to be taken by mouth to treat Stress Urinary Incontinence (SUI) in women.

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.

YENTREVE is believed to work by increasing the strength of the muscle that holds back urine when you laugh, sneeze, or perform physical activities.

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

2. What you need to know before you take YENTREVE

DO NOT take YENTREVE if you:

- are allergic to duloxetine or any of the other ingredients of this medicine (listed in section 6)
- have liver disease
- have severe kidney disease
- are taking or have taken within the last 14 days, another medicine known as a monoamine oxidase inhibitor (MAOI) (see 'Other medicines and YENTREVE')
- are taking fluvoxamine which is usually used to treat depression, ciprofloxacin or enoxacin which are used to treat some infections

Talk to your doctor if you have high blood pressure or heart disease. Your doctor will tell you if you should be taking YENTREVE.

Warnings and Precautions

The following are reasons why YENTREVE may not be suitable for you. Talk to your doctor before you take Yentreve if you:

- are taking medicines to treat depression (see 'Other medicines and YENTREVE')
- are taking St. John's Wort, a herbal treatment (*Hypericum perforatum*)
- have kidney disease
- have had seizures (fits)
- have had mania
- suffer from bipolar disorder
- have eye problems, such as certain kinds of glaucoma (increased pressure in the eye)
- have a history of bleeding disorders (tendency to develop bruises)
- are at risk of low sodium levels (for example if you are taking diuretics, especially if you are elderly)
- are currently being treated with another medicine which may cause liver damage.
- are taking other medicines containing duloxetine (see 'Other medicines and YENTREVE')

YENTREVE may cause a sensation of restlessness or an inability to sit or stand still. You should tell your doctor if this happens to you.

Thoughts of suicide and worsening of depression or anxiety disorder

Although YENTREVE 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 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
- 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

If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away.

You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet. You might ask them to tell you if they think your depression or anxiety is getting worse, or if they are worried about changes in your behaviour.

Children and adolescents under 18 years of age

YENTREVE should not be used for children and adolescents under 18 years. Also, you should know that patients under 18 have an increased risk of side-effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behaviour and anger) when they take this class of medicines. Also, the long-term safety effects concerning growth, maturation, and cognitive and behavioural development of YENTREVE in this age group have not yet been demonstrated.

Other medicines and YENTREVE

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

The main ingredient of YENTREVE, duloxetine, is used in other medicines for other conditions:

- diabetic neuropathic pain, depression, anxiety and urinary incontinence

Using more than one of these medicines at the same time should be avoided. Check with your doctor if you are already taking other medicines containing duloxetine.

Your doctor should decide whether you can take YENTREVE with other medicines. **Do not start or stop taking any medicines, including those bought without a prescription and herbal remedies, before checking with your doctor.**

You should also tell your doctor if you are taking any of the following:

Monoamine oxidase inhibitors (MAOIs): You should not take YENTREVE if you are taking or have recently taken (within the last 14 days) an antidepressant medicine called a monoamine oxidase inhibitor (MAOI). Examples of MAOIs include moclobemide (an antidepressant) and linezolid (an antibiotic). Taking a MAOI together with many prescription medicines, including YENTREVE, can cause serious or even life-threatening side effects. You must wait at least 14 days after you have stopped taking an MAOI before you can take YENTREVE. Also, you need to wait at least 5 days after you stop taking YENTREVE before you take a MAOI.

Medicines that cause sleepiness: These include medicines prescribed by your doctor including benzodiazepines, strong painkillers, antipsychotics, phenobarbital and sedative antihistamines.

Medicines that increase the level of serotonin: 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). These medicines increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with YENTREVE, you should see your doctor.

Oral anticoagulants or antiplatelet agents: Medicines which thin the blood or prevent the blood from clotting. These medicines might increase the risk of bleeding.

YENTREVE with food, drink and alcohol

YENTREVE may be taken with or without food. You should take extra care if you drink alcohol while taking YENTREVE.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

- Tell your doctor if you become pregnant, or you are trying to become pregnant, while you are taking YENTREVE. You should use YENTREVE only after discussing the potential benefits and any potential risks to your unborn child with your doctor.

Make sure your midwife and/or doctor knows you are on YENTREVE. When taken during pregnancy, similar drugs (SSRIs) may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

If you take YENTREVE near the end of your pregnancy, your baby might have some symptoms when it is born. These usually begin at birth or within a few days of your baby being born. These symptoms may include floppy muscles, trembling, jitteriness, not feeding properly, trouble with breathing and fits. If your baby has any of these symptoms when it is born, or you are concerned about your baby's health, contact your doctor or midwife who will be able to advise you.

- Tell your doctor if you are breast-feeding. The use of YENTREVE while breastfeeding is not recommended. You should ask your doctor or pharmacist for advice.

Driving and using machines

YENTREVE may make you feel sleepy or dizzy. Do not drive or use any tools or machines until you know how YENTREVE affects you.

YENTREVE contains sucrose

YENTREVE contains **sucrose**. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take YENTREVE

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

YENTREVE is for oral use. You should swallow your capsule whole with a drink of water.

The recommended dose of YENTREVE is 40 mg twice a day (in the morning and late afternoon/evening). Your doctor may decide to start your treatment with 20 mg twice a day for two weeks before increasing the dose to 40 mg twice a day.

To help you remember to take YENTREVE, you may find it easier to take it at the same times every day.

Do not stop taking YENTREVE, or change your dose, without talking to your doctor. Treating your disorder properly is important to help you get better. If it is not treated, your condition may not go away and may become more serious and difficult to treat.

If you take more YENTREVE than you should

Call your doctor or pharmacist immediately if you take more than the amount of YENTREVE prescribed by your doctor. Symptoms of overdose include sleepiness, coma, serotonin syndrome (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), fits, vomiting and fast heart rate.

If you forget to take YENTREVE

If you miss a dose, take it as soon as you remember. However, if it is time for your next dose, skip the missed dose and take only a single dose as usual. Do not take a double dose to make up for a forgotten dose. Do not take more than the daily amount of YENTREVE that has been prescribed for you in one day.

If you stop taking YENTREVE

DO NOT stop taking your capsules without the advice of your doctor even if you feel better. If your doctor thinks that you no longer need YENTREVE he or she will ask you to reduce your dose over 2 weeks.

Some patients, who suddenly stop taking YENTREVE after more than 1 week of therapy, have had symptoms such as:

- dizziness, tingling feelings like pins and needles or electric shock-like feelings (particularly in the head), sleep disturbances (vivid dreams, nightmares, inability to sleep), fatigue, sleepiness, feeling restless or agitated, feeling anxious, feeling sick (nausea) or being sick (vomiting), shaking (tremor), headaches, muscle pain, feeling irritable, diarrhoea, excessive sweating or vertigo.

These symptoms are usually not serious and disappear within a few days, but if you have symptoms that are troublesome you should ask your doctor for advice.

If you have further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. These effects are normally mild to moderate and often disappear after a short time.

Very common side effects (may affect more than 1 in 10 people)

- feeling sick (nausea), dry mouth, constipation
- fatigue

Common side effects (may affect up to 1 in 10 people)

- lack of appetite
- trouble sleeping, feeling agitated, less sex drive, anxiety, difficulty sleeping
- headache, dizziness, feeling sluggish, feeling sleepy, tremor, numbness, including numbness, pricking or tingling of the skin
- blurred eyesight
- feeling of dizziness or “spinning” (vertigo)
- increased blood pressure, flushing
- diarrhoea, stomach pain, being sick (vomiting), heartburn or indigestion
- increased sweating
- weakness, shivering

Uncommon side effects (may affect up to 1 in 100 people)

- throat inflammation that causes a hoarse voice
- allergic reactions
- decreased thyroid gland activity which can cause tiredness or weight gain
- dehydration
- grinding or clenching the teeth, feeling disorientated, lack of motivation, difficulty or failure to experience orgasm, unusual dreams
- feeling nervous, difficulty concentrating, changes in sense of taste, poor sleep quality
- large pupils (the dark centre of the eye), problems with eyesight, eyes feel dry
- tinnitus (hearing sound in the ear when there is no external sound), ear pain
- feeling the heart pumping in the chest, fast and/or irregular heart beat
- fainting
- increased yawning
- vomiting blood, or black tarry stools (faeces), gastroenteritis, inflammation of the mouth, burping, difficulty swallowing, breaking wind, bad breath
- inflammation of the liver that may cause abdominal pain and yellowing of the skin or whites of the eyes
- (itchy) rash, night sweats, hives, cold sweats, increased tendency to bruise
- muscle pain, muscle tightness, muscle spasm, contraction of the jaw muscle
- difficulty to start urinating, painful urination, needing to pass urine during the night, frequent urination, abnormal urine odour
- abnormal vaginal bleeding, menopausal symptoms
- chest pain, feeling cold, thirst, feeling hot
- weight loss, weight gain
- Yentreve may cause effects that you may not be aware of, such as increases in liver enzymes or blood levels of potassium, creatine phosphokinase, sugar, or cholesterol

Rare side effects (may affect up to 1 in 1000 people)

- serious allergic reaction which causes difficulty in breathing or dizziness with swollen tongue or lips
- low levels of sodium in the blood (mostly in elderly people; the symptoms may include feeling dizzy, weak, confused, sleepy or very tired, or feeling or being sick, more serious symptoms are fainting, fits or falls), syndrome of inappropriate secretion of anti-diuretic hormone (SIADH)
- suicidal behaviour, suicidal thoughts, mania (over activity, racing thoughts and decreased need for sleep), hallucinations, aggression and anger
- “Serotonin syndrome” (a rare reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), fits, sudden involuntary jerks or twitches of the muscles, sensation of restlessness or an inability to sit or stand still, difficulty controlling movement e.g. lack of coordination or involuntary movements of the muscles, restless legs syndrome
- increased pressure in the eye (glaucoma)
- dizziness, lightheadedness or fainting on standing up, cold fingers and/or toes
- throat tightness, nose bleeds

- passing bright red blood in your stools, inflammation of the large intestine (leading to diarrhoea)
- liver failure, yellowing of the skin or whites of the eyes (jaundice)
- Stevens-Johnson syndrome (serious illness with blistering of the skin, mouth, eyes and genitals), serious allergic reaction which causes swelling of the face or throat (angioedema), sensitivity to sunlight
- muscle twitching
- difficulty or inability to pass urine, needing to pass more urine than normal, having a decreased urine flow
- abnormal periods, including heavy, painful, irregular or prolonged periods, unusually light or missed periods, abnormal production of breast milk
- falls (mostly in elderly people), abnormal gait

Very rare side effects (may affect up to 1 in 10,000 people)

- inflammation of the blood vessels in the skin (cutaneous vasculitis)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the [national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store YENTREVE

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton.

Store in the original package to protect from moisture. Do not store above 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away of medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What YENTREVE contains

The **active** substance is duloxetine.

Each capsule contains 20 or 40 mg of duloxetine (as hydrochloride).

The **other** ingredients are:

Capsule content: hypromellose, hypromellose acetate succinate, sucrose, sugar spheres, talc, titanium dioxide (E171), triethyl citrate (*See end of section 2 for further information on sucrose*).

Capsule shell: gelatin, sodium lauryl sulfate, titanium dioxide (E171), indigo carmine (E132), red iron oxide and yellow iron oxide, edible black ink.

Edible ink: synthetic black iron oxide (E172), propylene glycol, shellac.

What YENTREVE looks like and contents of the pack

YENTREVE is a hard gastro-resistant capsule. Each capsule of YENTREVE contains pellets of duloxetine hydrochloride with a covering to protect them from stomach acid.

YENTREVE is available in 2 strengths: 20 and 40 mg.

The 40 mg capsules are orange and blue and are printed with '40 mg' and the code '9545'.

The 20 mg capsules are blue and are printed with '20 mg' and the code '9544'.

YENTREVE 40 mg is available in packs of 28, 56, 98, 140 and 196 (2 x 98) capsules.

YENTREVE 20 mg is available in packs of 28, 56 and 98 capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

Manufacturer: Lilly S.A., Avda. De la Industria, 30, 28108 Alcobendas, Madrid, Spain.

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Detailed information on this medicine is available on the European Medicines Agency web site: <http://www.ema.europa.eu>.