Patient Leaflet in Accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a physician's prescription only

Yentreve 20 mg
Capsules

Active ingredient:
duloxetine (as hydrochloride) 20 mg

Yentreve 40 mg
Capsules

Active ingredient:
duloxetine (as hydrochloride) 40 mg

Inactive ingredients and allergens in the preparation: See chapter 6 "*Additional information*" and chapter 2 section "*Important information about some of this medicine's ingredients".*

Read the entire leaflet carefully before using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, please contact your doctor or pharmacist.

This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar.

This medicine is intended for women above the age of 18.

Even though **Yentreve** is not indicated to treat depression, the active ingredient in this preparation (duloxetine) is used as an antidepressant.
Antidepressants increase the risk of suicidal behavior and thoughts in children, adolescents and young adults.
When beginning treatment with this medicine, patients of all ages and their relatives, must monitor behavioral changes such as worsening of depression, suicidal thoughts, aggressiveness etc.
If changes such as these occur, contact the doctor immediately.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Yentreve is intended to treat moderate to severe Stress Urinary Incontinence (SUI) in women.

Therapeutic group:
Serotonin and norepinephrine reuptake inhibitors (SNRIs) in the nervous system.

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).

Yentreve is taken orally.

2. BEFORE USING THIS MEDICINE

Do not use this medicine if:

- you are sensitive (allergic) to duloxetine or any of the other ingredients this medicine contains (listed in chapter 6 “Additional information”).
- you have liver disease.
- you have severe kidney disease.
- you are taking or have taken within the last 14 days, another medicine known as a monoamine oxidase inhibitor (MAOI) (see chapter 2, under section ‘Drug interactions’)
- you 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**.

Special warnings regarding the use of this medicine
Before initiating treatment with Yentreve, tell your doctor if:

- you are taking medicines to treat depression (see chapter 2, under section ‘Drug interactions’).
- you are taking St. John’s Wort, an herbal treatment (Hypericum perforatum).
- you have kidney disease.
- you have had or have seizures (fits).
- you have had or have mania.
- you suffer from bipolar disorder.
- you have eye problems, such as certain kinds of glaucoma (increased pressure in the eye).
- you have a history of bleeding disorders (tendency to develop bruises), especially if you are pregnant (see chapter 2, under section “Pregnancy and breastfeeding”).
- you are at risk of low sodium levels (for example if you are taking diuretics, especially if you are elderly).
- you are currently being treated with another medicine which may cause liver damage.
- you are taking other medicines containing duloxetine (see chapter 2, under section ‘Drug interactions’).

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.

You should also contact your doctor:

If you experience signs and symptoms of restlessness, hallucinations, loss of coordination, fast heartbeat, increased body temperature, fast changes in blood pressure, overactive reflexes, diarrhoea, coma, nausea, vomiting, as you might be suffering a serotonin syndrome.

In its most severe form, serotonin syndrome can resemble Neuroleptic Malignant Syndrome (NMS). Signs and symptoms of NMS may include a combination of fever, fast heartbeat, sweating, severe muscle stiffness, confusion, increased muscle enzymes (determined by a blood test).

Medicines like **Yentreve** (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction (see chapter 4). In some cases, these symptoms have continued after stopping treatment.

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 behavior 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 behavior.

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 adolescents under 18 have an increased risk of side effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, oppositional behavior 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.

Drug interactions:
If you are taking or have recently taken any other medicines, including nonprescription medicines and nutritional supplements, inform your doctor or pharmacist. In particular, inform your doctor if you are taking:
- 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 an MAOI together with additional 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 an 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 breastfeeding
If you are pregnant or breastfeeding, 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 breath 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 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.
- If you take **Yentreve** near the end of your pregnancy, there is an increased risk of excessive vaginal bleeding shortly after birth, especially if you have a history of bleeding disorders. Your doctor or midwife should be aware that you are taking duloxetine so they can advise you.
- Available data from the use of **Yentreve** during the first three months of pregnancy do not show an increased risk of overall birth defects in general in the child. If **Yentreve** is taken during the second half of pregnancy, there may be an increased risk that the infant will be born early (6 additional premature infants for every 100 women who take **Yentreve** in the second half of pregnancy), mostly between weeks 35 and 36 of pregnancy.
- Tell your doctor if you are breastfeeding. 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.

Important information about some of this medicine's ingredients:
Yentreve contains sucrose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking **Yentreve**.
Each duloxetine 20 mg capsule contains: 12.0 mg sucrose and 27 mg sugar spheres.
Each duloxetine 40 mg capsule contains: 24.2 mg sucrose and 54 mg sugar spheres.

Yentreve contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

3. HOW TO USE THIS MEDICINE?

Always use according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about the dosage and manner of treatment with this medicine.
The dosage and manner of treatment will be determined only by your doctor.
The recommended dose of **Yentreve** is usually 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.

Yentreve is for oral use. You should swallow your capsule whole with a drink of water.
Yentreve contains enteric-coated pellets that prevents their dissolution in the stomach. Therefore, do not chew or crush the contents of the capsule and do not open the capsule and sprinkle the contents on food or mix with liquids. This is to prevent the effect of food or drink on the enteric coating. Furthermore, the medicine is not meant to be taken via a nasogastric tube since contents of the capsule may obstruct the tube.

To help you remember to take **Yentreve**, you may find it easier to take it at the same time every day.

Do not exceed the recommended dose.

If you have accidently taken a higher dose you must contact your doctor or pharmacist immediately. 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 have taken an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a doctor or a hospital Emergency Room and bring the package of the medicine with you.

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.

You must continue with the treatment as recommended by your doctor.
Even if there is an improvement in your health condition, do not discontinue the treatment with this medicine without consulting your doctor or pharmacist.

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 stop taking Yentreve
Do not stop taking your capsules without consulting 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.

Do not take medicines in the dark! Check the label and dose <u>each time</u> you take a medicine. Wear glasses if you need them.

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

4. SIDE EFFECTS

As with any medicine, using **Yentreve** can cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not suffer from any of 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.
- diarrhea, 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 disoriented, 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 heartbeat.
- fainting.

- increased yawning.
- vomiting blood, or black tarry stool (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 odor.
- 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 1,000 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 behavior, 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, light-headedness or fainting on standing up, cold fingers and/or toes.
- throat tightness, nose bleeds.
- coughing, wheezing and shortness of breath which may be accompanied by a high temperature.
- passing bright red blood in your stools, inflammation of the large intestine (leading to diarrhea).
- 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.
- excessive vaginal bleeding shortly after birth (postpartum hemorrhage).
- 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).

Side effects whose frequency is not known (cannot be estimated from the available data)
- signs and symptoms of a condition called “stress cardiomyopathy” which may include chest pain, shortness of breath, dizziness, fainting, irregular heartbeat.

If a side effect appears, if one of the side effects becomes worse, or if you suffer from a side effect not mentioned in this leaflet, you must consult your doctor.

Reporting of side effects
Side effects can be reported to the Ministry of Health by clicking on the link “Reporting side effects due to drug treatment” that can be found on the Home Page of the Ministry of Health’s website (www.health.gov.il), which refers to the online form for reporting side effects, or via the following link: https://sideeffects.health.gov.il

5. HOW TO STORE THIS MEDICINE

- **Avoid poisoning!** This medicine, and any other medicine, must be stored in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
- Do not use the medicine after the expiry date (exp**.** date) which is stated on the carton. The expiry date refers to the last day of that month.
- **Storage conditions**: Store at a temperature below 25°C.
- Store in the original package in order to protect the medicine from moisture.
- Do not throw away the medicine via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. ADDITIONAL INFORMATION

In addition to the active ingredient, this medicine also contains:
Sugar spheres, talc, hypromellose acetate succinate (HPMCAS), sucrose, color mixture White DDB8257W, hypromellose 2910, triethyl citrate.

What does the medicine look like and contents of the pack:
Yentreve is a hard gastro-resistant capsule. Each capsule of **Yentreve** contains pellets of duloxetine hydrochloride with an enteric coating that protects them from stomach acid.

Yentreve is marketed in two dosages: 20 mg and 40 mg.
The 20 mg capsules are blue and are printed with “20 mg” and the code “9544”.
The 40 mg capsules are orange and blue and are printed with “40 mg” and the code “9545”.

Yentreve 20 mg and 40 mg capsules are supplied in packages of 7, 14, 28, 56 capsules.
Not all pack sizes may be marketed.

License holder and address: Eli Lilly Israel Ltd., 4 HaSheizaf St., POB 4246 Ra’anana 4366411, Israel

Manufacturer name and address: Lilly S.A., Alcobendas, Madrid, Spain.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Yentreve 20 mg: 132-68-31140-12
Yentreve 40 mg: 132-69-31141-12

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