PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS, 1986)

The medicine is marketed according to a doctor's prescription only.

CIPRALEX® Tablets
10 mg, 15 mg, 20 mg

Composition: the active ingredient and its quantity:

- Cipralex 10 mg: each film coated tablet contains 10 mg escitalopram (as oxalate)
- Cipralex 15 mg: each film coated tablet contains 15 mg escitalopram (as oxalate)
- Cipralex 20 mg: each film coated tablet contains 20 mg escitalopram (as oxalate)

Inactive Ingredients: See section 6.

- **Read the entire leaflet carefully before using the medicine.** This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or the pharmacist.
- This medicine was prescribed for you. Do not pass it on to others. It can harm them even if it seems to you that their medical state is similar.
- The medicine is not usually intended for children and adolescents under the age of 18.

Antidepressants and anti-anxiety medications increase the risk of suicidal thoughts and behavior in children, adolescents, and young adults up to 25 years old.
In patients of all ages who start taking this medicine, the patients and their relatives should monitor behavioral changes such as worsening of depression, suicidal thoughts, aggression and other similar changes. In case such changes occur, contact your doctor immediately.

1. WHAT IS THE MEDICINE INTENDED FOR?

Cipralex is an antidepressant that belongs to the selective serotonin reuptake inhibitors (SSRIs) group. These medicines act on the serotonin-system in the brain by increasing the serotonin level.
Cipralex is used to treat the following conditions:
Depression .
Panic Disorder.
Generalized Anxiety Disorder (GAD).
Social anxiety disorder (SAD) (Social Phobia).
Obsessive-compulsive disorder.

It may take a few weeks until you start to feel better.
Continue taking the medicine even if it takes some time before you feel any improvement.
Consult with your doctor if you do not feel any improvement or if you feel worse.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient or any of the other ingredients that the medicine contains (see the list of inactive ingredients in section 6).
- You take other medicines which belong to the non-selective, irreversible, monoamine oxidase inhibitors (MAOI) group such as phenelzine, iproniazide, isocarboxazide, nialamide, tranylcypromine. Cipralex may be started 14 days after discontinuing treatment with MAO inhibitors and at least 7 days should elapse after discontinuing Cipralex treatment before starting treatment with MAO inhibitors.

  Also, Cipralex should not be taken concomitantly with reversible monoamine oxidase inhibitors type MAO-AI

  (such as moclobemide, used in the treatment of depression), or the non-selective, reversible monoamine oxidase inhibitor (MAOI) linezolid (an antibiotic) or the irreversible monoamine oxidase inhibitors type MAOI-B (such as selegiline, used in the treatment of Parkinson´s disease). The combination with these medicines may increase the risk for Serotonine syndrome (see section "Drug interactions").
- You suffer from abnormal heart rhythm (as examined by ECG; an examination to evaluate how the heart is functioning) or from a congenital defect in the electrical functioning of the heart.
- You take medicines for heart rhythm problems or that may affect the heart's rhythm (see section "Drug interactions").
- You take the medicine pimozide.

Special warnings regarding use of the medicine

Before starting treatment with Cipralex, tell your doctor if:

- You are pregnant or breast feeding (See section 'Pregnancy, breastfeeding and fertility').
- If you are suffering, or have suffered in the past from epilepsy. Treatment with Cipralex should be stopped if seizures occur for the first time, or if there is an increase in seizure frequency (see also section "Side effects").
- If you are suffering, or have suffered in the past from impaired liver or kidney function. The doctor may need to adjust your dosage.
- You have diabetes. Treatment with Cipralex may alter glycaemic control. Insulin and/or oral hypoglycaemic dosage may need to be adjusted.
- You have a decreased level of sodium in the blood.
- You have a tendency to easily develop bleedings or bruises, or if you are pregnant (see 'Pregnancy, breast-feeding and fertility').
- You are receiving electroconvulsive treatment (ECT).
- You are suffering, or have suffered in the past from coronary heart disease.
- You suffer or have suffered in the past from heart problems or have recently had a heart attack.
- You have a low resting heart-rate and/or you know that you may have salt depletion as a result of prolonged severe diarrhoea and vomiting (being sick) or usage of diuretics.
- You experience a fast or irregular heartbeat, fainting, collapse or dizziness on standing up, which may indicate abnormal functioning of the heart rate.
- If you have or have previously had eye problems, such as certain kinds of glaucoma (increased

pressure in the eye).

Please note:
Some patients with manic-depressive illness may enter into a manic phase. This is characterized by unusual and rapidly changing ideas, inappropriate happiness and excessive physical activity. If you experience these symptoms, contact your doctor.

Symptoms such as restlessness or difficulty to sit or stand still can also occur during the first weeks of the treatment. Tell your doctor immediately if you experience these symptoms.

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

Panic disorder
In the treatment of panic disorder it usually takes 2-4 weeks before any improvement is seen. In the beginning of the treatment certain patients may experience increased anxiety, which generally resolves during the first 1-2 weeks.
Therefore, a low starting dose is recommended in panic disorder. Therefore, it is very important that you strictly follow your doctor's orders and do not stop the treatment or change the dose without consulting your doctor.

Thoughts of suicide and worsening of the depression or the anxiety disorder
Suicidal thoughts or thoughts of harming oneself are common in psychiatric disorders especially in patients suffering from depression and/or have an anxiety disorder. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

These kinds of thoughts are more likely to occur:
- If you have previously had thoughts about killing or harming yourself.
- If you 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.**
It is recommended 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
Cipralex is not usually intended for children and adolescents under the age of 18 years. Patients under 18 have an increased risk of side effects such as suicide attempts, suicidal thoughts and hostility (predominately aggression, oppositional behaviour and anger) when they take this class of medicines. Despite this, your doctor may prescribe Cipralex for patients under 18 because he decides that this is in their best interest. If your doctor has prescribed Cipralex for a patient under 18 and you want to discuss this, please go back to your doctor. You should inform your doctor if any symptoms listed above develop or worsen when patients under 18 are taking Cipralex. Also, the long term safety effects concerning growth, maturation and cognitive and behavioural development of Cipralex in this age group have not yet been demonstrated.

Drug Interactions:

If you are taking, or have recently taken, other medicines, including nonprescription medicines and nutritional supplements, tell the doctor or pharmacist. It is especially important to inform the doctor or pharmacist if you are taking:

- ”Non-selective monoamine oxidase inhibitors (MAOIs)” (such as: phenelzine, iproniazid, isocarboxazid, nialamide, and tranylcypromine). If you have taken any of these medicines you will need to wait 14 days before you start taking Cipralex. After stopping Cipralex you must allow 7 days before taking any of these medicines.
- Do not use with reversible, selective monoamine oxidase A inhibitors (MAO-AI) such as moclobemide (used to treat depression).
- Do not use with irreversible monoamine oxidase inhibitors B (MAO-BI) such as selegiline (used to treat Parkinson’s disease). These may increase the risk of side effects.
- Do not use with the antibiotic linezolid.
- Lithium (used in the treatment of manic-depressive disorder) and tryptophan.
- Imipramine and desipramine (used to treat depression).
- Sumatriptan and similar medicines (used to treat migraine) and tramadol and similar medicines (opioids, used against severe pain). These may increase the risk of side effects.
- Cimetidine, lansoprazole and omeprazole (used to treat stomach ulcers), fluconazole (used to treat fungal infections), fluvoxamine (antidepressant) and ticlopidine (used to reduce the risk of stroke). These may cause increased blood levels of escitalopram.
- St. John's Wort (Hypericum perforatum) - a herbal remedy used for the treatment of depression.
- Aspirin (Acetylsalicylic acid) and non-steroidal anti-inflammatory drugs (medicines used for pain relief or to thin the blood, so called anti-coagulant). These may increase bleeding-tendency.
- Warfarin, dipyridamole, and phenprocoumon (medicines used to thin the blood, so called anti-coagulant). The doctor will probably check the coagulation time of your blood when starting and discontinuing Cipralex in order to verify that your dose of anti-coagulant is still adequate.
- Medicines that may lower the threshold for seizures: Mefloquine (used to treat Malaria), bupropion (used to treat depression) and tramadol (used to treat severe pain).
- Neuroleptics (medicines to treat schizophrenia and psychosis) and antidepressants (tricyclic antidepressants and SSRIs) due to a possible risk of a lowered threshold for seizures.
- Flecainide, propafenone, and metoprolol (used in cardiovascular diseases) clomipramine, and nortriptyline (antidepressants) and risperidone, thioridazine, and haloperidol (antipsychotics). The dosage of Cipralex may need to be adjusted.
- Medicines that decrease blood levels of potassium or magnesium as these conditions increase the risk of life threatening heart rhythm disorder.

Do not take Cipralex concomitantly with medicines for heart rhythm problems or medicines that may affect the heart’s rhythm, such as Class IA and III antiarrhythmics, antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol), tricyclic antidepressants, certain antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, anti-malarial treatment particularly halofantrine), certain antihistamines (e.g. astemizole, hydroxyzine, mizolastine). If you have any further questions about this you should speak to your doctor.
- Antidepressant drugs of the SSRI and SNRI groups, may cause a serotonin syndrome (rare) that includes symptoms such as nervousness, agitation, confusion, sweating, high fever, increased reflexes, muscle cramps, tremor, tachycardia (see 'Side Effects').
The syndrome is more likely to appear in patients who take additional drugs that affect the nervous system (see above) concomitantly. The doctor must be informed about any additional drug that you may take.

Use of the medicine and food
The medicine can be taken with or without food.

Use of the medicine and alcohol consumption
As with many medicines, combining Cipralex with alcohol is not advisable, although Cipralex is not expected to interact with alcohol.

Pregnancy, breast-feeding and fertility
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.
Do not take Cipralex if you are pregnant or breast-feeding unless you and your doctor have discussed the risks and benefits involved.
If you take Cipralex during the last 3 months of your pregnancy, the following effects may be seen in your newborn baby: trouble with breathing, blue-ish skin, fits, body temperature changes, feeding difficulties, vomiting, low blood sugar, stiff or floppy muscles, vivid reflexes, tremor, jitteriness, irritability, lethargy, constant crying, sleepiness and sleeping difficulties. If your newborn baby has any of these symptoms, please contact your doctor immediately.
Make sure your midwife and/or doctor know you are on Cipralex. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like Cipralex 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 Cipralex near the end of your pregnancy there may be an increased risk of heavy 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 Cipralex so they can advise you.
If used during pregnancy Cipralex should never be stopped abruptly.
Escitalopram might be excreted into breast milk and therefore it is not recommended to nurse while using Cipralex. Citalopram, a medicine like escitalopram, has been shown to reduce the quality of sperm in animal studies. Theoretically, this could affect fertility, but impact on human fertility has not been observed as yet.

Driving and using machines
You are advised not to drive a car or operate machinery, or engage in any other activity that requires alertness, until you know how Cipralex affects you.

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

3. HOW SHOULD YOU USE THE MEDICINE?
Always use according to the doctor's instructions. You should check with the doctor or pharmacist if you are not sure. The dosage and treatment regimen will be determined by the doctor only. The usual dose is:
Adults
Depression: The normally recommended dose is 10 mg once daily (single daily dose). The dose may be increased by your doctor to a maximum of 20 mg per day.
Panic disorder: The starting dose of Cipralex is 5 mg once daily (single daily dose) for the first week before increasing the dose to 10 mg per day. The dose may be further increased by your

doctor to a maximum of 20 mg per day.
Social anxiety disorder: The normally recommended dose of Cipralex is 10 mg once daily (single daily dose). Your doctor can either decrease your dose to 5 mg per day or increase the dose to a maximum of 20 mg per day, depending on how you respond to the medicine.
Generalised anxiety disorder: The normally recommended dose of Cipralex is 10 mg once daily (single daily dose). The dose may be increased by your doctor to a maximum of 20 mg per day.
Obsessive-compulsive disorder: The normally recommended dose of Cipralex is 10 mg once daily (single daily dose). The dose may be increased by your doctor to a maximum of 20 mg per day.

Elderly patients (above 65 years of age)
The recommended starting dose of Cipralex is 5 mg once daily (single daily dose). The dose may be increased by your doctor to 10 mg per day.

Children and adolescents
Cipralex should not normally be given to children and adolescents. (See section "2. Before using the medicine").

Reduced kidney function
Caution is advised in patients with severely reduced renal function. Take as prescribed by your doctor.

Reduced liver function
Patients with liver complaints should not receive more than 10 mg per day. Take as prescribed by your doctor.

Patients known to be poor metabolisers of the enzyme CYP2C19
Patients with this known genotype should not receive more than 10 mg per day. Take as prescribed by your doctor.

Do not exceed the recommended dosage.

Directions for Use:
Swallow the medicine with some water. Do not chew or crush the tablet, as the taste is bitter!
Take the medicine with or without food.
It is possible to divide the tablet.
If necessary, you can divide the tablets 10, 15 and 20 mg by firstly placing the tablet on a flat surface with the score facing upwards. The tablet may then be broken by pressing down on each end of the tablet, using both forefingers as shown in the drawing.

The tablets 10, 15 and 20 mg can be divided into equal doses.

Duration of treatment
It may take a few weeks before you start to feel better. Continue to take Cipralex even if it takes

some time before you feel any improvement in your condition. Do not change the dose of your medicine without consulting the doctor first.
Complete the course of treatment according to the doctor's recommendation. Stopping the treatment too soon, may cause the symptoms to return. It is recommended that treatment should be continued for at least 6 months after you feel well again.

- **If you accidentally took an overdose, or if a child has accidentally swallowed the medicine,** proceed immediately to the doctor or to a hospital emergency room, and bring the package with you. Do this even if there are no signs of discomfort. Possible symptoms of an overdose could be: dizziness, tremor, agitation, convulsion, coma, nausea, vomiting, change in heart rhythm, decreased blood pressure and change in body fluid/salt balance.
- **If you forget to take this medicine at the specified time, do not take a double dose.** If you do forget to take a dose, and you remember before you go to bed, take it straight away. Carry on as usual the next day. If you only remember during the night, or the next day, leave out the missed dose and carry on as usual.
- Complete the treatment as recommended by the doctor. This medicine should be taken at specified time intervals as determined by the attending doctor. Even if there is an improvement in your well-being, do not stop the treatment with this medicine without consulting the doctor or the pharmacist.
- **If you stop taking Cipralex:**

Do not stop taking Cipralex until your doctor tells you to do so. When you have completed the course of treatment, it is generally advised that the dose of Cipralex is gradually reduced over a number of weeks.
Stopping the treatment abruptly may cause discontinuation symptoms, which are common when treatment with Cipralex is stopped. The risk is higher, when Cipralex has been used for a long time or in high doses or when the dose is reduced too quickly. Most people find that the symptoms are mild and go away on their own within two weeks.
However, in some patients they may be severe in intensity or they may be prolonged (2-3 months or more). If you get severe discontinuation symptoms when you stop taking Cipralex, please consult the doctor. The doctor may ask you to start taking your tablets again and come off them more slowly.
Discontinuation symptoms include: Feeling dizzy (unsteady or off-balance), feelings like pins and needles, burning sensations and (less commonly) electric shock sensations, including in the head, sleep disturbances (vivid dreams, nightmares, inability to sleep), feeling anxious, headaches, feeling sick (nausea), sweating (including night sweats), feeling restless or agitated, tremor (shakiness), feeling confused or disorientated, feeling emotional or irritable, diarrhea (loose stools), visual disturbances, fluttering or pounding heartbeat (palpitations).

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

If you have any further questions regarding the use of the medicine, consult the doctor or pharmacist.

4. Side Effects:

As with all medicines, use of Cipralex may cause side effects in some users. Do not be alarmed when reading the list of side effects; you may not experience any of them.
The side effects usually disappear after a few weeks of treatment. Please be aware that many of the effects may also be symptoms of your illness and therefore will improve when you start to get better.

Contact your doctor or go to the hospital straight away, if you experience the following symptoms:

Uncommon (may affect up to 1 in 100 people):

- Unusual bleeds, including gastrointestinal bleeds

Rare (may affect up to 1 in 1000 people):

- Swelling of skin, tongue, lips, pharynx or face, hives or have difficulties breathing or swallowing (serious allergic reaction).
- High fever, agitation, confusion, trembling and abrupt contractions of muscles these may be signs of a rare condition called serotonin syndrome.

Not known (frequency cannot be estimated from the available data):

- Difficulties urinating
- Seizures (fits), see also section **"special warning regarding use of the medicine"**
- Yellowing of the skin and the white in the eyes are signs of liver function impairment/hepatitis
- Fast, irregular heart beat, fainting which could be symptoms of a life-threatening condition known as Torsade de Pointes
- Thoughts of harming yourself or killing yourself, see also section "**special warning regarding use of the medicine**"
- Sudden swelling of skin or mucosa (angioedemas)
- Cases of rhabdomyolysis (skeletal muscle break downs) were reported post marketing. Contact your doctor immediately if you experience an unexplained muscle pain, tenderness or muscle weakness.

In addition to above the following side effects have been reported:

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

- Feeling sick (nausea)
- Headache

Common (may affect up to 1 in 10 people):

- Blocked or runny nose (sinusitis)
- Decreased or increased appetite
- Anxiety, restlessness, abnormal dreams, difficulties falling asleep, feeling sleepy, dizziness, yawning, tremors, prickling of the skin
- Diarrhoea, constipation, vomiting, dry mouth
- Increased sweating
- Pain in muscle and joints (arthralgia and myalgia)
- Sexual disturbances (delayed ejaculation, problems with erection, decreased sexual drive and women may experience difficulties achieving orgasm)
- Fatigue, fever
- Increased weight

Uncommon (may affect up to 1 in 100 people):

- Rash, itching (pruritus)
- Grinding one's teeth, agitation, nervousness, panic attack, confusion state
- Disturbed sleep, taste disturbance, fainting (syncope)
- Enlarged pupils (mydriasis), visual disturbance, ringing in the ears (tinnitus)

- Loss of hair
- Excessive menstrual bleeding
- Irregular menstrual period
- Decreased weight
- Fast heart beat
- Swelling of the arms or legs
- Nosebleeds

Rare (may affect up to 1 in 1000 people):
- Aggression, depersonalisation, hallucination
- Slow heart beat

Not known (frequency cannot be estimated from the available data):
- Decreased levels of sodium in the blood (the symptoms are feeling sick and unwell with weak muscles or confused)
- Dizziness when you stand up due to low blood pressure (orthostatic hypotension)
- Abnormal liver function test (increased amounts of liver enzymes in the blood)
- Movement disorders (involuntary movements of the muscles)
- Painful erections (priapism)
- Signs of abnormal bleeding e.g. from skin and mucous (ecchymosis) and low level of blood platelets (thrombocytopenia)
- Increased secretion of a hormone called ADH, causing the body to retain water and dilute the blood, reducing the amount of sodium (inappropriate ADH secretion)
- Increased blood levels of the hormone prolactin
- Flow of milk in men and in women that are not nursing
- Mania
- An increased risk of bone fractures has been observed in patients taking this type of medicines
- Alteration of the heart rhythm (called “prolongation of QT interval”, seen on ECG, measuring electrical activity of the heart).
- Heavy vaginal bleeding shortly after birth (postpartum haemorrhage), see ‘Pregnancy, breast-feeding and fertility’ in section 2 for more information.

In addition, a number of side effects are known to occur with drugs that work in a similar way to escitalopram (the active ingredient of Cipralex). These are:
Motor restlessness (akathisia)
Loss of appetite

If any of the side effects gets worse, or if you suffer from any side effects not listed in the leaflet, consult the doctor.

Reporting of side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Adverse Drug Reactions Report" that appears on the home page of the Ministry of Health web site (www.health.gov.il), which leads to an online form for reporting side effects. Alternatively you can use the following link: https://sideeffects.health.gov.il/

5. HOW SHOULD THE MEDICINE BE STORED?

Avoid poisoning! This medicine and all other medicines must be kept in a closed place out

of the reach of children and/ or infants to avoid poisoning. Do not induce vomiting without explicit instructions from the doctor!

- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** Store at a temperature below 30°C.

6. ADDITIONAL INFORMATION

In addition to the active ingredient, the medicine also contains:
Talc, Croscarmellose Sodium, Microcrystalline Cellulose silicifide, Magnesium Stearate, Purified water, Opadry OY-S-28849 (white)

- What Cipralex looks like and contents of the pack:

10 mg: Oval, white film-coated tablets. The tablets are scored and marked with “E” and “L” on each side of the score on one side of the tablet.
15 mg: Oval, white film-coated tablets. The tablets are scored and marked with “E” and “M” on each side of the score on one side of the tablet.
20 mg: Oval, white film-coated tablets. The tablets are scored and marked with “E” and “N” on each side of the score on one side of the tablet.

The tablets 10, 15 and 20 mg can be divided into equal doses.

The tablets are presented in blister packs that contain 7, 14, 28, 56, 98 tablets. Not all pack sizes may be marketed.

Registration holder: Lundbeck Israel Ltd., 11 Galgaley Haplada, P.O.B. 13105, Herzliya 4672211.
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Manufacturer: H. Lundbeck A/S, Ottiliavej 9, DK-2500 Valby , Denmark.

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Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Cipralex 10 mg film coated tablets 127.01.30558
Cipralex 15 mg film coated tablets 127.02.30559
Cipralex 20 mg film coated tablets 127.03.30560