PACKAGE LEAFLET: INFORMATION FOR THE USER

Exenadil®
20 mg and 40 mg film-coated tablets
40 mg/ml oral drops, solution
Citalopram

1. IDENTIFICATION OF THE MEDICINAL PRODUCT

1.1 Trade name

Exenadil®, film-coated tablets 20 mg, 40 mg.
Exenadil®, oral drops solution 40 mg/ml.

1.2 Composition

Film-coated tablet
Active substance: Citalopram hydrobromide
Excipients: Lactose monohydrate, Starch maize pregelatinized, Cellulose microcrystalline, Glycerol, Copovidone, Croscarmellose sodium, Magnesium stearate.
Coating: Hypromellose (Methocel E5 premium EP), Titanium dioxide CI 77891 E 171, Macrogol 400.

Oral drops, solution
Active substance: Citalopram hydrochloride
Excipients: Methylparaben E218, Propylparaben E216, Hydroxyethylcellulose, Ethanol 96%, Water purified
Oral drops solution contains alcohol 9.0% v/v.

1.3. Pharmaceutical form

Film-coated tablets.
Oral drops, solution.

1.4. Quantitative composition

Each film-coated tablet contains respectively 20 mg, or 40 mg of citalopram.

Each ml of oral drop solution contains citalopram hydrochloride 44.48 mg corresponding to citalopram 40 mg. (1 drop = 2 mg).

1.5. Nature and contents of container

Film-coated tablets 20 mg or 40 mg
White, round, scored tablets, contained in transparent blisters of PVC & Aluminum foil. Each blister bares product details, lot number and contains 14 tablets. Each package contains 2 blisters, i.e. 28 tablets and a leaflet.

Oral drops solution
Aqueous solution in a bottle of 15ml, baring screw safety cap and dropper. A label on the bottle bares product details and lot information. Each carton contains one bottle and a leaflet.

1.6. Pharmacotherapeutic category

Antidepressant.

1.7. Marketing Authorization Holder

TARGET PHARMA
54 Menandrou st., 104 31, Athens, Greece
Tel.: +30 210 52 24 830, Fax: +30 210 52 24 838,
E-mail: info@targetpharma.gr, www.targetpharma.gr.

1.8. Manufacturer

A. KLEVA SA- Pharmaceutical Industry
189 Parnithos Av. - 13675 Acharnai Attica Greece
Tel.: +30 210 24 02 404–7

B. HELP SA (manufacturing and primary packaging)

2. WHAT SHOULD THE PATIENT KNOW ABOUT THIS MEDICINE

2.1. General infformation

Exenadil® contains citalopram, a bicyclic phthalene derivative with antidepressant action. Citalopram is a selective serotonin reuptake inhibitor.

2.2. Indications

- Major depressive episode. Prophylactic treatment against relapses and new depressive episodes.
- Panic disorder with or without agoraphobia.
- Obsessive–compulsive disorder.

2.3. Contraindications

Hypersensitivity to the active substance or any of the excipients of the product.
Concurrent or recent administration (less than 14 days) of MAO inhibitors.

2.4. Special warnings and precautions for use

2.4.1. General

Citalopram should not be administered to patients treated with MAO inhibitors at least 14 days after discontinuation. MAO inhibitors should not be administered but at least 7 days after citalopram discontinuation.

Some patients with panic disorders may experience intense anxiety symptoms at the beginning of the treatment. This paradoxical initial increase in anxiety is more pronounced during the first days of treatment and retreats with the continuation of the treatment (within 2 weeks).

Hemorrhage
Caution is recommended to patients that receive anti-coagulant treatment together with citalopram, or medicines that affect platelet function (e.g. NSAIDs, acetylsalicylic derivatives, ticlopidine, dipyridole) or other medicines that increase the hemorrhage risk. Caution is also recommended to patients baring a history of bleeding disorders.

Suicidal thoughts and worsening of depression or panic disorder
If you have depression or anxiety disorder, you may sometimes have thoughts of harming yourself or commit suicide. These thoughts may be increased during the initiation of treatment with antidepressants, as all medicines need some time to act, usually about two weeks or sometimes longer.

It is more likely to have such thoughts:
- If you previously had suicidal thoughts or you were thinking to harm yourself.
- If you are a young adult. Information from clinical trials has shown increased risk of suicidal behavior in adults younger than 25 years with psychological disorders receiving antidepressant treatment.
Whenever you have thoughts of harming yourself or suicidal thoughts, **contact your doctor or go to a hospital immediately.**

It might be helpful to inform a relative or a close friend, that you have depression or anxiety disorder and ask them to read this leaflet. You may ask them to tell you if they believe that your condition has worsened or if they worry about you behavioral changes.

Pharmaceutical dependence and withdrawal
Until today, there no pre-clinical or clinical evidence that Selective Serotonin Reuptake Inhibitors are addictive.
However, with regard to withdrawal, abrupt discontinuation of these medications may cause some symptoms (dizziness, hallucinations, headache, nausea, anxiety) which though are mild and transient. For this reason, it is recommended that the discontinuation of the treatment should be gradual and always according to the doctor's instructions.

In general, as it is very difficult using experimental models to accurately predict individual patient's response to CNS acting substances, special care should be taken when these drugs are going to be administered to patients with history of psychiatric drug abuse.

2.4.2. Elderly

Patients older than 65 years should receive half of the recommended dose.

2.4.3. Pregnancy – Lactation

Citalopram safety during pregnancy has not been established. For this reason **Exenadil®** should not be used during pregnancy or lactation unless the expected benefit for the patient exceeds the theoretical risk for the fetus or breast-fed infant.

2.4.4. Children

Use in children and adolescents under 18 years of age
Exenadil® should not be used in children and adolescents under 18 years of age. You should also know that patients younger than 18 years, when they receive this pharmaceutical category, have increased risk of presenting side-effects, such as suicidal attempts, suicidal thoughts, hostile behavior (mainly aggression, opposing behavior and anger). Despite that, your doctor may prescribe **Exenadil®** to patients younger than 18 years, if they consider that this is for the benefit of the patient. If the doctor prescribed **Exenadil®** to a patient younger than 18 years, and you wish to discuss this, ask your doctor for more information. You should inform you doctor immediately, if any of the above mentioned effects is presented or worsens, since **Exenadil®** is administered to a patient younger than 18 years. It should be noted that until today there are no long-term data on **Exenadil®'s** safety with regard to physical development, maturation, mental and behavioral development of this age group.

2.4.5. Effect on the ability to drive and use machines

Citalopram has little effect on cognitive and psychomotor performance and interaction with alcohol is not significant. But in patients, who are prescribed psychotropic medications, an effect on attention and concentration may be expected and these patients should be accordingly warned. Otherwise, everything depends on patient's reaction to the drug. It should be considered by the doctor.

2.4.6. Special warnings about the excipients

See section 2.3.

2.5. Interactions with other medicines or substances

Concomitant administration of MAO inhibitors may cause hypertensive crises and constitute a contraindication.
Caution is required in co-administration with lithium or tryptophan and with serotonergic drugs (e.g. sumatriptan).

It is not recommended to combine this medicine with alcohol.

Co-administration with products containing St. John's Wort/Hypericum perforatum, may lead to increased side effects.

A small increase in citalopram's plasma levels has been observed when received in combination with certain phenothiazines (levomepromazine) but with no clinical importance.

Medicinal products that affect hemostasis
Co-administration with coagulant medicines that affect platelet function (e.g. NSAIDs, acetylsalicylics, ticlopidine, dipyridamole) or other medicines that affect hemostasis, due to the increased risk for hemorrhage.

2.6. Posology

Citalopram tablets are administered as a single dose once daily preferably at night.
Citalopram drops are also administered once daily.
Oral drops can be mixed with water, orange juice or apple juice.

Citalopram oral drops solution presents 25% higher bioavailability compared to tablets. Consequently doses of tablets correspond to doses of drops as follows:

Tablets	Oral drops
10 mg	8 mg (4 drops)
20 mg	16 mg (8 drops)
30 mg	24 mg (12 drops)
40 mg	32 mg (16 drops)
60 mg	48 mg (24 drops)

Major depressive episode. Prophylactic treatment against relapses and new depressive episodes.
Film-coated tablets
The usual dose is 20mg once daily. If clinically indicated, the dose may be increased to 40 mg and, if necessary, up to 60 mg daily. Patients over 65 years of age should receive half of the recommended dose, i.e. 10-30mg daily.

Oral drops solution
The drops of citalopram are orally administered once daily as a dose of 16 mg (8 drops). The response of each patient in the treatment and the severity of depression will determine whether the dose will be increased to the maximum of 48 mg (24 drops) daily.

Elderly patients over 65 years of age should receive half of the recommended dose, i.e. from 8 mg (4 drops) to 24 mg (12 drops) daily.

The antidepressant effect is established within 2 to 4 weeks. Treatment with antidepressants is symptomatic and should therefore be continued for an appropriate period of time, usually 4-6 months, to stabilize the effect and prevent recurrences. Patients suffering from recurrent depression may need to continue treatment for a number of years to avoid new episodes of depression.

Panic disorder

Film-coated tablets
Initial dose: 10mg daily. After one week the dose can be increased to 20mg daily. The optimal dose is 20-30 mg daily. In case of insufficient response, the dose may be increased up to a maximum of 60 mg daily.

Oral drops solution
Initial dose: 8 mg (4 drops) daily. After one week the dose can be increased to 16 mg (8 drops) daily. The optimal dose is 16-24 mg (8-12 drops). In case of insufficient response the dose may be increased up to a maximum of 48 mg (24 drops) daily.

Elderly patients over 65 years of age should receive half of the recommended dose.

Treatment for panic disorder is long-term. Maintenance of the therapeutic effect has been reported during prolonged treatment (1year).

Obsessive-compulsive disorder

Film-coated tablets
Recommended initial daily dose: 20mg. The dose may be increased gradually by 20mg until maximum dose of 60mg daily, if this is needed.

Oral drops solution
Recommended initial daily dose: 16 mg (8 drops). The dose may be increased gradually by 16 mg (8 drops) until maximum dose of 48 mg (24 drops) daily, if this is necessary.

Elderly patients aged over 65 years, should receive half of the recommended dose.

The onset of action in the treatment of obsessive compulsive disorder occurs within 2-4 weeks and the improvement increases over time.

Children: **Exenadil®** should not be used for the treatment of children and adolescents younger than 18 years of age. (se section 2.4.).

Patients with Liver impairment
Adult patients with liver impairment should receive the minimum recommended dose and should be carefully monitored.

Patients with Renal deficiency
Dosage adjustments are not required to patients with mild or moderate renal impairment. There is no experience to patients with severe renal impairment (creatinine clearance < 20 ml/min).

2.7. Overdose - Management

Symptoms
Mild poisoning (<600 mg):
Fatigue, weakness, sedation, dizziness, trembling hands, nausea, cold sweat.

Severe poisoning – maximum dose reported 1.800-2.000 mg, about 45-50 times the average daily dose:
Symptoms were apathy evolving into lethargy, a crisis of non-specific muscle spasms, cyanosis, faint and noisy breathing probably due to aspiration, and vaginal tachycardia (pulse rate 128).

Management
Overdose management should be symptomatic and supportive. A gastric lavage should take place as soon as possible after oral administration. Respiratory tracks should be kept open with intubation if

needed. In cases of hypoxemia administration of oxygen is needed and in cases of convulsios administration of diazepam. Medical surveillance for at least 24 hours is recommended. There is no specific antidote, but the patient can benefit from the administration of a serotonin antagonist (e.g. methylsergide).

Poison Center Athens, Tel.: +30 210 77 93 777.

2.8. Possible side effects

Adverse effects that are reported during the use of **Exenadil®** are in general few, mild and transient. Most common are nausea, somnolence, increased sweating, dry mouth and tremor.
Such effects are more evident during the first two weeks of the treatment and then are decreased as the depression is improved.

Rare cases of bleeding have been reported, such as brushing, vaginal bleeding, and hemorrhage of GI tract or mucosal tissue.
An increased risk of bone-fractures has been also reported among patients receiving this medicine.

The following side effects have been reported with citalopram:

Common:
Skin and subcutaneous system disorders: increased sweating.
Central and Peripheral Nervous system disorders: headache, tremor, dizziness.
Visual disorders: eye adjustment disorder
Psychiatric disorders: somnolence, insomnia, irritability, nervousness.
Gastrointestinal disorders: nausea, dry mouth, constipation, diarrhea.
Cardiovascular disorders: palpitation
General disorders: weakness.

Uncommon:
Skin and subcutaneous tissue disorders: rash, pruritis.
Central and Peripheral Nervous system disorders: paraesthesia, migraine.
Senses disorders: visual disturbances, taste alterations.
Psychiatric disorders: sleep disturbances, decreased libido, decreased attention, abnormal dreams, amnesia, anxiety, increased appetite, anorexia, apathy, impotence, suicidal attempt, confusion, yawning.
Gastrointestinal disorders: dyspepsia, vomiting, abdominal pain, flatulence, salivation.
Metabolism and nutrition disorders: weight loss, weight gain.
Vascular disorders: orthostatic hypotension.
Cardiovascular disorders: tachycardia.
Respiratory disorders: rhinitis.
Urogenital disorders: polyuria, urinary disorders.
Reproductive system disorders female: anorgasmia.
Reproductive system disorders male: ejaculation disorders
General disorders: fatigue.

Rare:
Muscle skeletal disorders: myalgia.
Central and Peripheral Nervous system disorders: extrapyramidal disorders, convulsions.
Senses disorders: tinnitus.
Psychiatric disorders: euphoria, increased libido.
Respiratory disorders: cough.
General disorders: malaise.

If you get any side effects, please talk to your doctor or pharmacist or any other health care provider or directly to the National Medicines Agency (284 Mesogion Av., 15562, Cholargos, Athens, Greece www.eof.gr).

2.9. What should the patient know if forgets to take one dose

If you must get this medicine and you forget one dose, you should take the missed dose as soon as you remember. If it is near the time for your next dose, do not take the forgotten dose, continue your treatment as planned.

2.10. What should the patient know about the expiration date

Indicated in inner and outer packaging. Do not use this medicine after this date.

Oral drops solution should be used within 16 weeks after first opening of the package if kept at temperature below 25°C.

2.11. Special warnings about the storageof the product

This medicine should be kept at room temperature. Keep it in the initial container and out of reach and sight of children.

Exenadil® oral drops solution should be kept at temperature below 25°C.

2.12. Date of last revision of this leaflet

September 2014 (according to the MA of the product and EOF's Circular No. 31269/13-5-2008).

3. INFORMATION FOR THE RATIONAL USE OF MEDICINES

- This pharmaceutical product was prescribed by your doctor to you, according to your medical history and condition. Do not pass the product to others or use it in any other condition even if the symptoms may appear the same and without receiving your doctor's or pharmacist's advice.
- If during treatment with this medicine you experience any problem or issue, contact immediately your doctor or pharmacist.
- If you have any questions regarding the information for this product, its use or about the medical condition that you suffer, you should ask your doctor or pharmacist.
- This product will be safe and effective if it is used exactly according to instructions provided.
- For your own safety it is highly recommended that you read carefully all information provided for the prescribed medicine.
- Do not store medicines in bathroom lockers, as the high temperature and the humidity may degrade the product which may be harmful to your health.
- Store the product in the original packaging.
- If your doctor instructed you to stop the use of this product, dispose the remaining product and do not use it.
- Do not keep the medicine you do not need any more or those that are expired.
- Keep all medicines in safe place out of reach and sight of children.

4. PRESCRIBING INFORMATION

This medicine is subjected to medicinal prescription.