Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Miln-Avenir 25 mg
Miln-Avenir 50 mg
Capsules

Active ingredient
Each capsule contains milnacipran 25/50 mg
Inactive ingredients and allergens: See section 6 "Additional information".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

Antidepressants and anti-anxiety medicines increase the risk of suicidal behavior and thoughts in children, adolescents and young adults up to the age of 25.
Upon starting treatment with the medicine, patients of all ages and their relatives must follow behavioral changes, such as depression worsening, suicidal thoughts, aggression, etc.
If such changes occur, contact your doctor immediately.

1. What is this medicine intended for?
For treatment of depression in adults above the age of 18 years.

Therapeutic group: SNRI (Serotonin Noradrenaline Reuptake Inhibitor) antidepressants

The effect of Miln-Avenir is visible after a certain period of time varying from 1 to 3 weeks.

2. Before using this medicine

Do not use this medicine if:

- You are allergic to the active ingredient or to any of the other ingredients in this medicine (see section 6).
- You are already taking other medicines for treatment of depression: irreversible monoamine oxidase inhibitors (iproniazid, nialamide).
- You are already taking certain medicines for treatment of Parkinson's disease: selective monoamine oxidase-B-inhibitors (selegiline).
- You are already taking certain medicines affecting the heart (digitalis (digoxin)).
- You are already taking certain medicines for treatment of migraines (sumatriptan and other medicines of the same group).
- You are breastfeeding.
- You have high blood pressure and you are not being treated or if you have severe or unstable coronary heart disease.

Special warnings about using this medicine

Do not generally take Miln-Avenir if:
- You are already taking certain medicines affecting the cardiovascular system (adrenaline or noradrenaline administered by injection, clonidine and similar medicines).

- You are already taking certain medicines for treatment of depression (moclobemide, toloxatone).
- You have difficulty urinating due to an enlarged prostate (benign prostatic hyperplasia) or if you have other genitourinary disorders.

Additional warnings
Medicines like Miln-Avenir (called SSRIs/SNRIs) may cause symptoms of sexual dysfunction (see section 4). In some cases, these symptoms have lasted after stopping treatment.

Suicidal thoughts and worsening of depression or anxiety disorder
If you suffer from depression and/or anxiety disorders, you may sometimes experience thoughts of self-injury (hurting yourself) or suicide. These symptoms may worsen when first starting treatment with antidepressants, since the effect of these medicines does not appear immediately, but only after 2 weeks of treatment or more.
You are more likely to experience these type of symptoms in the following cases:
- If you have experienced suicidal thoughts or thoughts of self-injury in the past.
- If you are a young adult. Clinical studies have shown an increased risk of suicidal behavior in adults below the age of 25 with a psychiatric illness and being treated with an antidepressant.

If you experience suicidal thoughts or a thought of self-injury, contact your doctor or go directly to a hospital. You can get help from a friend or relative by explaining that you are depressed or have an anxiety disorder and asking them to read this leaflet. You can ask them to inform you if they think that the depression or anxiety is worsening, or if they are worried about changes in your behavior.

Talk to your doctor before taking Miln-Avenir, especially if you have a history of bleeding disorders or if you are pregnant (see “Pregnancy, breastfeeding and fertility”).

Inform your doctor in the event of:
- Serotonin syndrome: it may include digestive symptoms (diarrhoea), changes in psychiatric state and behavior (agitation, confusion, a milder form of mania), motor dysfunction (tremor, rigidity, muscle twitching, overactive reflexes, disturbance of motion coordination) or autonomic instability (unstable blood pressure, fast heart rate, shivering, increased body temperature, possible coma).
- Insomnia or nervousness at the beginning of treatment.
- Kidney failure: your doctor may need to change your daily dose.
- An enlarged prostate (benign prostatic hyperplasia) or difficulty urinating or other genitourinary disorders.
- High blood pressure (hypertension) or heart disease.
- Vision disorders related to an increase in the fluid pressure in the eyes (narrow-angle glaucoma).
- Epilepsy or a history of epilepsy.
- Mania
- Jaundice (yellowing of the skin and whites of the eyes) or liver dysfunction.

In view of the risk of hyponatremia (a decrease in the level of sodium in the blood): Caution is advised in the elderly, patients taking diuretics or other treatment known to induce hyponatremia and patients with cirrhosis or malnutrition.

Children and adolescents
Milnacipran is not intended for use in children and adolescents below the age of 18 years.

Drug interactions

If you are taking or have recently taken other medicines, including non-prescription medications and dietary supplements, tell your doctor or pharmacist.
Do not take this medicine in combination with:

- certain other medicines for treatment of depression (irreversible monoamine oxidase inhibitors), such as iproniazid, nialamide.
- certain medicines for treatment of Parkinson's disease (selective monoamine oxidase B inhibitors, such as selegiline).
  You must wait at least 14 days after you have stopped taking monoamine oxidase inhibitors before you can take Miln-Avenir. Also, you have to wait at least 7 days after you stop taking Miln-Avenir before taking monoamine oxidase inhibitors.
- certain medicines affecting the heart (digitalis (digoxin)).
- certain medicines for treatment of migraines (sumatriptan and other medicines of the same group).
- certain medicines affecting the cardiovascular system (adrenaline or noradrenaline administered by injection, clonidine and similar medicines).
- certain other medicines used for treatment of depression (linezolid, moclobemide, toloxatone, methylene blue).

Unless recommended by your doctor, do not take this medicine in combination with:

- certain other medicine that may increase the risk of bleeding (NSAIDs, aspirin).
- lithium

Certain other medicines can also affect the way Miln-Avenir works

- Diuretics

Using this medicine and food
Take this medicine with a glass of water, preferably with food.

Using this medicine and alcohol consumption
Consumption of alcoholic beverages or medicines containing alcohol is not recommended.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to become pregnant, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
It is not recommended to take this medicine if you are a woman of childbearing potential and are not using contraception or if you are pregnant. If you discover that you are pregnant during treatment, consult your doctor, as only he/she can decide whether or not treatment should be continued.
If you are taking Miln-Avenir until delivery, your baby may present with reversible symptoms related to withdrawal syndrome or exposure to milnacipran immediately or soon after delivery. In this case, clinical surveillance is required.
Consult your doctor or pharmacist before taking any medicines.

If you take Miln-Avenir near the end of pregnancy, there may be an increased risk of heavy vaginal bleeding shortly after delivery, especially if you have a history of bleeding disorders. Your doctor or midwife should be aware that you are taking Miln-Avenir, so they will be able to advise you.

Breastfeeding
This medicine may pass into breast milk. Therefore, it is contraindicated during breastfeeding. Consult your doctor or pharmacist before taking any medicines.

Fertility

Animal fertility is affected by milnacipran.
No data are available on the effect of milnacipran on human fertility.

Driving and using machines
This medicine may cause dizziness, especially at the beginning of treatment. If you experience this side effect, do not drive vehicles or operate machines requiring attention.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. The usual dose is 1 capsule of 50 mg in the morning and 1 capsule of 50 mg in the evening, preferably with a meal.

If you suffer from renal insufficiency, the recommended dose is reduced according to the degree of alteration in renal function. In this case, use the 25 mg capsules. Your doctor will determine the dose appropriate for you.

Do not exceed the recommended dose.
Swallow the capsules with a glass of water, preferably with food.

Treatment duration
The treatment usually lasts for several months.
Do not stop the treatment yourself even if your condition has improved. If necessary, the treatment must be stopped gradually in accordance with your doctor's instructions (see sub-section "If you stop taking the medicine" and section 4 "Side effects").

There is no information regarding opening and dispersing the capsule.

If you take more Miln-Avenir than you should
If you take more of this medicine than you should, talk to a doctor or go to a hospital immediately. Take the medicine package with you, even if there are no tablets left.
Medical treatment may be necessary.

If you forget to take Miln-Avenir at the scheduled time, do not take a double dose to make up for a forgotten dose.
Adhere to the treatment as recommended by your doctor.

If you stop taking the medicine
Do not stop taking Miln-Avenir, unless your doctor has ordered you to do so. Since withdrawal symptoms may occur after the end of treatment, a gradual dose reduction is recommended. The withdrawal symptoms are usually mild to moderate and resolve spontaneously; however, in some patients, they may be severe in intensity and prolonged (2-3 months or more).

Do not take medicines in the dark! Check the label and dose every time you take a medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects

Like with all medicines, using Miln-Avenir may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Side effects can occur especially during the first week or the first two weeks of treatment with milnacipran.

Contact your doctor immediately if you develop any of the following side effects:

- A rash or an allergic reaction, such as itching, swelling of the lips and/or tongue or wheezing and/or shortness of breath, **stop taking the capsules and contact your doctor immediately.**
- Sudden weakness or numbness in the face, arms or legs, particularly on one side only, or speech difficulties (symptoms of a cerebrovascular accident).
- Heart problems, such as chest pain (sensation of tension, tightness, squeezing).
- A group of symptoms related to excess serotonin in the brain (serotonin syndrome) due to significant effects of Miln-Avenir manifested by high fever, nausea, excessive sweating, anxiety, hot flushes, muscle twitching or tremor, palpitations and restlessness. This syndrome is observed mainly in patients taking other medicines simultaneously.

Additional side effects

<u>Very common side effects - effects affecting more than one in ten users</u>

- Headache, nausea

<u>Common side effects - effects affecting up to one in ten users</u>

- Agitation, anxiety, depression, eating disorders, sleep disorders, suicidal behavior
- Migraines, tremor, dizziness, changes in sensitivity, somnolence
- Feeling the heartbeats (palpitations), faster heart rate (tachycardia), increased blood pressure, hot flushes
- Abdominal pain, diarrhoea, constipation, dry mouth, indigestion, vomiting
- Itching, rash, excessive sweating
- Muscle pain
- Inability to urinate, abnormally frequent urination (pollakiuria)
- Erectile dysfunction, ejaculation disorders, testicular pain
- Fatigue

<u>Uncommon side effects - effects affecting up to one in one hundred users</u>

- Hypersensitivity
- Increased level of lipids in the blood, weight loss
- Feelings of panic, confusion, delusion, strange visions or sounds (hallucinations), hyperactive behavior or thoughts (mania), decreased libido, abnormal dreams, suicidal thoughts
- Memory problems, feeling restless (akathisia), balance problems, taste changes, loss of consciousness (syncope)
- Blurred vision, dry eyes, pain in the eyes, decreased visual acuity, dilated pupils (mydriasis), accommodation disorders
- Sensation of dizziness or spinning (vertigo), ringing or buzzing in the ears (tinnitus)
- Heart problems, such as low blood pressure, conduction disorders
- Poor blood circulation, causing numbness and discoloration in fingers and toes (Raynaud's syndrome), orthostatic hypotension
- Difficulties breathing, cough, dry nose, throat diseases
- Gastrointestinal disorders, such as stomach inflammation (gastritis), mouth inflammation (stomatitis), abdominal discomfort, abdominal distension, ulcers, hemorrhoids, colon inflammation (colitis)
- Abnormal liver function tests
- Skin disease (dermatosis), allergic skin reactions (hives), skin inflammation (dermatitis)
- Muscle pain or stiffness
- Urinary disorders, such as urination disorders, urinary retention, urinary incontinence, possibly red-colored urine

- Some women may have heavy menstrual bleeding or no menstrual period
- Prostate disorders
- Feeling abnormal, pain, chills

Rare side effects - effects affecting up to one in one thousand users

- Anaphylactic shock
- Inappropriate secretion of a hormone controlling urine volume (syndrome of inappropriate antidiuretic hormone secretion)
- Psychotic disorders, derealization (thinking disorder)
- Involuntary movements (dyskinesia), parkinsonism (a medical term that can include many symptoms, such as increased secretion of saliva, musculoskeletal stiffness, limited or abnormal body movements, lack of facial expression, muscle tightness, shaking), convulsion
- Heart-related pain behind the sternum, which can radiate into the environment (angina pectoris)
- Hepatitis, hepatocellular damage
- Sensitivity to sunlight (photosensitivity reaction)

Side effects of unknown frequency (the frequency of these effects has not been established yet)

- A decrease in the level of sodium in the blood (hyponatremia)
- Bleeding in the skin and mucous membranes
- Convulsions, especially in patients with a history of epilepsy
- Serotonin syndrome
- Aggression
- Cytolytic hepatitis
- Stevens-Johnson syndrome (a serious disseminated illness with blistering of the skin and the mucous membranes)
- Takotsubo cardiomyopathy (stress cardiomyopathy)
- Heavy vaginal bleeding shortly after delivery (postpartum hemorrhage), see "Pregnancy, breastfeeding and fertility" in section 2 for more information.

Some symptoms can also be caused by depression.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il/

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package/blister. The expiry date refers to the last day of that month.
  Storage conditions
- Do not store above 25°C.
- Do not throw away any medicine via wastewater or household waste. Ask the pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient, this medicine also contains:
Capsule core:
calcium hydrogen phosphate dihydrate, carmellose calcium, povidone K30, colloidal anhydrous silica, magnesium stearate, talc.
The capsule shell contains:
gelatin, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172).

What the medicine looks like and contents of the pack:
Miln-Avenir 25 mg: caramel opaque hard capsules containing white or almost white powder.
Miln-Avenir 50 mg: red caramel opaque hard capsules containing white or almost white powder.
The capsules are available in aluminium/PVC/PVDC blister.
Packs of 14, 28 and 56 capsules.
Not all pack sizes may be marketed.

Registration holder's name and address: BioAvenir Ltd., 1 David Hamelech St., Herzliya Pituach 4666101.

Manufacturer's name and address: Rivopharm SA, Centro Insema 6928 Manno, Switzerland

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Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Miln-Avenir 25 mg: 169-70-36192-00
Miln-Avenir 50 mg: 169-71-36193-00