PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986
The medicine is dispensed with a doctor's prescription only

Miro 30, 45
Tablets

Composition:
Each **Miro 30** tablet contains:
Mirtazapine 30 mg
Each **Miro 45** tablet contains:
Mirtazapine 45 mg

For the list of inactive and allergenic ingredients in the preparation, see section 2 "Important information about some of the ingredients in **Miro**" and section 6 - "Further Information".

Read the leaflet carefully in its entirety before using the medicine.
This leaflet contains concise information about **Miro.** If you have further questions, ask your doctor or pharmacist.
This medicine has been prescribed to treat 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.
This medicine is not intended for use in children and adolescents below the age of 18 years.

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.
When starting treatment with the medicine, patients of all ages and their relatives must monitor for behavioral changes such as: worsening of depression, suicidal thoughts, aggression and the like.

1. WHAT IS THE MEDICINE INTENDED FOR?

Miro is used to treat depression.

Therapeutic group: A preparation from the SNRIs group.

2. BEFORE USING THE MEDICINE

Do not use Miro if:
- You are sensitive (allergic) to mirtazapine or to any of the other ingredients in this medicine (detailed in section 6). If so, talk to your doctor as soon as possible before starting to use **Miro.**
- You are taking, or have recently taken (within the past two weeks), medicines called monoamine oxidase inhibitors (MAOIs).

Do not take, or tell your doctor before taking **Miro**:
If you have ever developed a severe skin rash, skin peeling, blistering and/or mouth ulcers after taking **Miro** or other medicines.

Special warnings regarding use of Miro:
Before starting treatment with **Miro,** talk to your doctor or pharmacist.

Children and adolescents
Miro is not intended for use in children and adolescents below the age of 18, because efficacy has not been demonstrated. In addition, you should be aware that patients under the age of 18, who took medicines from this group have a higher risk of side effects such as suicide attempt, suicidal thoughts and hostility (predominantly aggression, opposition and anger). Nevertheless, your doctor may prescribe **Miro** to patients under the age of 18 because he decides it is for their benefit.

If your doctor prescribed **Miro** for a patient under the age of 18 and you want to discuss it with him, please refer back to your doctor. Inform the doctor if any of the symptoms listed above occur or worsen when patients under the age of 18 take **Miro**. In addition, the long-term effects of **Miro** in this age group regarding growth, sexual maturation and cognitive and behavioral development still have not been proven. Furthermore, during treatment with **Miro,** significant weight gain was more frequently observed in this age group as compared to adults.

Thoughts of suicide and worsening of your depression
If you are depressed, you can sometimes have thoughts of harming or killing yourself. These may be increased when first starting to take antidepressants, since all these medicines take time to start working, usually about two weeks, but sometimes longer.
You may be more likely to think like this:
- If you previously had thoughts of harming or killing yourself.
- If you are a young adult. Information from clinical trials has shown an increased risk of suicidal behavior in adults aged less than 25 with psychiatric conditions, who were treated with antidepressants.

If you have thoughts of harming or killing yourself at any time, contact your doctor or proceed directly to the hospital.

You may find it helpful to tell a relative or close friend that you are depressed; ask them to read this leaflet. You can ask them to tell you if they think your depression is getting worse or if they are concerned about changes in your behavior.

Also, caution should be taken with Miro if:
- You have, or have ever had, one of the following conditions (tell your doctor about these conditions before taking **Miro,** if you have not done so yet):
  - **Seizures** (epilepsy). If you develop seizures or your seizures become more frequent, stop taking **Miro** and contact your doctor immediately;
  - Serious skin reactions including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction accompanied by an increase in white blood cells (eosinophilia) and systemic symptoms (DRESS), which have been reported with the use of mirtazapine. If one or more of the listed symptoms occur, stop taking **Miro** and contact your doctor immediately. If you ever developed serious skin reactions, **do not** commence treatment with **Miro**.
  - **Liver disease,** including jaundice. If jaundice develops, stop taking **Miro** and contact your doctor immediately;
  - **Kidney disease;**
  - **Heart disease** or **low blood pressure;**
  - **Schizophrenia.** If psychotic symptoms, such as paranoid thoughts, become more frequent or worsen, contact your doctor immediately;
  - **Manic depression** (alternating periods of feeling elated/overactivity and depressed mood). If you start feeling elated or overexcited, stop taking **Miro** and contact your doctor immediately;
  - **Diabetes** (you may need to adjust your dose of insulin or the dosage of other antidiabetic medicines);
  - **Eye disease,** such as increased intraocular pressure in the eye (glaucoma);
  - **Difficulty in passing water** (urinating), which might be caused by an **enlarged prostate**;
  - **Certain heart conditions** which may change your heart rate, a recent heart attack, heart failure or if you are taking certain medicines that may affect the heart rate.
- You develop **signs of infection** such as high, inexplicable fever, sore throat and mouth ulcers.

Stop taking Miro and consult your doctor immediately regarding a blood test.
In rare cases, these symptoms can be signs of disturbances in blood cell production in the bone marrow. While rare, these symptoms most commonly appear after 4-6 weeks of treatment.
- You are an elderly person. You could be more sensitive to the side effects of antidepressants.

Drug interactions
If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the attending doctor or pharmacist.
Do not take Miro together with:
- **Monoamine oxidase inhibitors** (MAO inhibitors). In addition, do not take **Miro** during the first two weeks after discontinuing treatment with MAO inhibitors. Similarly, do not take MAO inhibitors during the two weeks after discontinuing treatment with **Miro.** Examples of MAO inhibitors are moclobemide, tranylcypromine (both are antidepressants) and selegiline (used for Parkinson's disease).

Exercise caution when taking **Miro** in combination with:
- **Antidepressants** e.g., **SSRIs, venlafaxine** and **L-tryptophan or triptans** (used to treat migraine), **tramadol** (analgesic), **linezolid** (antibiotic), **lithium** (for treatment of certain psychiatric conditions), **methylene blue** (to treat high blood methemoglobin levels), and **St. John's Wort -** preparations of **Hypericum perforatum** (a herbal medicine for depression). In very rare cases, **Miro** alone or in combination with these medicines may lead to a condition called serotonin syndrome. Some of the symptoms of this syndrome are: inexplicable fever, sweating, increased heart rate, diarrhea, muscle contractions (uncontrollable), tremor, overactive reflexes, restlessness, mood changes and unconsciousness. If you have a combination of these symptoms, talk to your doctor immediately.
- **Nefazodone antidepressant.** It may increase the amount of **Miro** in your blood. Inform your doctor if you are using this medicine. There may be a need to lower the dose of **Miro** or increase the dose of **Miro** again, after discontinuing treatment with nefazodone.
- **Medicines for anxiety or insomnia** e.g., benzodiazepines.
  Medicines for schizophrenia e.g., olanzapine.
  Medicines for allergy e.g., cetirizine.
  Medicines for severe pain e.g., morphine.
  In combination with these medicines, **Miro** may increase the drowsiness effect.
- **Medicines for infections;** medicines for bacterial infections (e.g., erythromycin), medicines to treat fungal infections (e.g., ketoconazole), and medicines to treat HIV/AIDS (e.g., HIV protease inhibitors), and **medicines for gastric ulcers** (e.g., cimetidine).
  In combination with **Miro,** these medicines may increase **Miro** levels in your blood. Inform your doctor if you are using these medicines. There may be a need to reduce the dose of **Miro** or to increase the dose of **Miro** again, after discontinuing these medicines.
- **Medicines for epilepsy** e.g., carbamazepine and phenytoin.
  Medicines for tuberculosis e.g., rifampicin.
  In combination with **Miro,** these medicines may reduce the amount of **Miro** in your blood. Inform your doctor if you are using these medicines. There may be a need to increase the dose of **Miro** or to reduce the dose of **Miro** again, after discontinuing these medicines.
- **Medicines to prevent blood clotting,** such as warfarin.
  Miro may increase the effects of warfarin on the blood. Inform your doctor if you are using this medicine.
  If taken together, it is recommended that the doctor carefully monitor coagulation functions.
- **Medicines which may affect the heart rate** such as certain antibiotics and certain antipsychotics.

Use of the medicine and alcohol consumption
You may be drowsy if you drink alcohol while taking **Miro.**
It is recommended not to drink alcohol at all.

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

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning a pregnancy, consult your doctor or pharmacist before taking this medicine.
Limited experience in administering **Miro** to pregnant women does not indicate an increased risk. Nevertheless, caution should be exercised when using during pregnancy.
If you are using **Miro** up until or shortly before birth, monitor your baby for possible side effects.
Make sure the midwife and/or doctor knows you are taking **Miro**.
When similar medicines (SSRIs) are taken during pregnancy, they may increase the risk of a severe medical condition in babies called persistent pulmonary hypertension of the newborn (PPHN), that causes the baby to breathe faster and to look bluish. These symptoms usually begin during the first 24 hours after birth of the baby. If this happens to your baby, contact your midwife and/or doctor immediately.

Driving and operating machinery
Miro may affect your concentration or alertness. Before driving or operating machinery, be sure that these abilities are not affected by taking **Miro**.

Important information about some of the ingredients in Miro
Miro tablets contain lactose.
If you have been told by your doctor that you have an intolerance to certain sugars, contact your doctor before taking this medicinal product (also see section 6).
Miro 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 **Miro** according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain regarding the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only.
The usual dosage is generally:
The usual starting dose is generally 15 or 30 mg every day. Your doctor may advise you, after several days, which dose is best for you (between 15-45 mg per day). The dose is usually the same for all ages. However, if you are elderly or if you have a kidney or liver disease, your doctor may adjust the dose accordingly.

Do not exceed the recommended dose.

When to take Miro
Take **Miro** at the same time every day. It is preferable to take **Miro** as a single dose before going to sleep. However, your doctor may advise you to split the **Miro** dose – once in the morning and once in the evening before going to sleep. The higher dose must be taken before going to sleep.
Take the tablets orally.
Swallow the tablet with a little water or juice.
If necessary, the tablet can be halved for immediate use. There is no information regarding crushing or chewing the tablet.

When you can expect to start feeling better:
Generally, Miro will start to work after 1-2 weeks and you may start to feel better after 2-4 weeks.
It is important that you talk to your doctor during the first weeks of treatment regarding the effects of **Miro:**
2-4 weeks after starting treatment with Miro, tell your doctor how the medicine affected you. If you still do not feel better, your doctor may prescribe a higher dose for you. In this case, talk to your doctor again after another 2-4 weeks.
You will usually have to continue taking **Miro** until the symptoms of your depression have disappeared for 4-6 months.

If you took more Miro than you needed
If you accidentally took a higher dosage of Miro, contact a doctor immediately.
The most common signs of **Miro** overdose (without other medicines or alcohol) are **drowsiness, disorientation and increased heart rate.**
If you took an overdose, or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take Miro
If you are supposed to take your dose **once a day**
- Do not take a double dose to compensate for the forgotten dose. Take the next dose at the regular time.

If you are supposed to take your dose **twice a day**
- If you forgot to take your morning dose, simply take it together with your evening dose.
- If you forgot to take your evening dose, do not take it with the following morning dose; simply skip it and continue with your regular morning and evening doses.
- If you forgot to take both doses, do not attempt to compensate for the forgotten doses. Skip the two doses and continue the next day with your regular morning and evening doses.

If you stopped taking Miro
Miro can only be discontinued after consulting with your doctor.
If you stop too early, your depression may recur. Talk to your doctor as soon as you feel better. The doctor will decide when you can stop treatment.
Do not stop taking **Miro** suddenly, even if your depression has passed. If you stop taking **Miro** suddenly, you may feel nauseous, dizzy, agitated or anxious, and you may have headaches. These symptoms can be prevented by gradual discontinuation. Your doctor will tell you how to lower the dose gradually.

How can you contribute to the success of the treatment?
Do not take medicines in the dark! Check the label and the dose each time you take medicine. Wear glasses if you need them.
If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of **Miro** may cause side effects in some users.
Do not be alarmed by reading the list of side effects. You may not suffer from any of them.
If you experience any of the following serious side effects, stop taking mirtazapine and tell the doctor immediately.

Common side effects (may affect 1 person in 10):
- Memory problems, which, in most cases, pass when treatment is discontinued.

Uncommon side effects (may affect up to 1 person in 100):
- Feeling elated or emotionally "high" (mania).

Rare side effects (may affect up to 1 person in 1,000):
- Yellow coloring of the eyes or skin; this may indicate disturbance in liver function (jaundice).
- Severe upper abdominal pain that sometimes occurs with nausea and vomiting (pancreatitis).

Side effects of unknown frequency (the frequency can not be estimated from the available data):
- Thoughts of harming or killing yourself – **contact your doctor immediately or go to a hospital straight away.**
- A skin reaction known as erythema multiforme (itchy reddish purple patches on the skin, especially on the palms of the hands or soles of the feet, 'hive-like' raised swollen areas on the skin, tender areas on the surfaces of the mouth, eyes and genitals, which may be accompanied by fever and tiredness).
- Severe rash, blisters (bullous dermatitis).
- Red lesions on the body, in the form of circular patches with a darker center (target-like), usually accompanied by blisters, peeling of the skin, ulcers of the mouth, throat, nose, eyes or genitals. This severe rash is preceded by fever and flu-like symptoms (symptoms of severe skin reaction called Stevens-Johnson syndrome or toxic epidermal necrolysis).
- Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or hypersensitivity syndrome).
- Signs of an infection such as high, inexplicable fever, sore throat or mouth ulcers (agranulocytosis). In rare cases, mirtazapine can cause disturbances in blood cell production (bone marrow depression). Certain people become less resistant to infection since mirtazapine can cause a temporary deficiency in white blood cells (granulocytopenia). In rare cases, mirtazapine can also cause a temporary red and white blood cell deficiency, in addition to platelets (aplastic anemia), a platelet deficiency (thrombocytopenia) or increase in the number of white blood cells (eosinophilia).
- An epileptic attack (seizures).
- A combination of symptoms such as high, inexplicable fever, sweating, increased heart rate, diarrhea, muscle contractions (uncontrolled), tremor, overactive reflexes, restlessness, mood changes, unconsciousness and increased salivation. In very rare cases, these can be signs of serotonin syndrome.
- Muscle pain, stiffness and/or weakness, in addition to darkened or discolored urine (rhabdomylosis).

Other possible side effects of mirtazapine are:
Very common (may affect more than 1 person in 10):
- Increased appetite and weight gain.
- Drowsiness or sleepiness.
- Headache.
- Dry mouth.

Common (may affect up to 1 person in 10):
- Lethargy.
- Dizziness.
- Instability or tremor.
- Nausea.
- Diarrhea.
- Vomiting.
- Constipation.
- Rash or skin eruptions (exanthema).
- Joint pain (arthralgia) or muscle pain (myalgia).
- Back pain.
- Feeling dizzy or faint when suddenly standing up (orthostatic hypotension).
- Swelling (generally in the ankles or feet) caused by fluid retention (edema).
- Fatigue.
- Vivid dreams.
- Confusion.
- Feeling anxious.
- Sleeping problems.

Uncommon (may affect up to 1 person in 100):
- Abnormal sensations in the skin, e.g., burning, stinging, tickling or numbness (paresthesia).
- Restlessness in the legs.
- Fainting (syncope).
- Numbness in the mouth (oral hyposensitivity).
- Low blood pressure.
- Nightmares.
- Feeling agitated.
- Hallucinations.
- Urge to move.

Rare (may affect up to 1 person in 1,000):
- Muscle twitching or contractions (myoclonus).
- Aggression.

Unknown (the frequency can not be estimated from the available data):
- Abnormal sensations in the mouth (oral paresthesia).
- Swelling in the mouth (oral edema).
- Swelling in the body (generalized edema).
- Localized swelling.
- Low levels of sodium in the blood (hyponatremia).
- Inappropriate secretion of a hormone that regulates the water levels in the blood (anti-diuretic hormone).
- Increased salivation.
- Sleepwalking (somnambulism).
- Speech disorders.
- Increased creatine kinase levels in the blood.
- Difficulty passing urine (urinary retention).
- Increase in blood prolactin hormone levels (hyperprolactinemia, including symptoms of enlarged breast and/or milk secretion from the nipples).

Additional side effects in children and adolescents
The following side effects were commonly observed in clinical studies in children under the age of 18 years: significant weight gain, urticaria and increased blood triglycerides.
If a side effect occurs, if one of the side effect worsens or if you suffer from a side effect not mentioned in the leaflet, consult with the doctor immediately.

Reporting side effects
Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il), that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il
Additionally, you can report to "Unipharm Ltd.".

5. HOW SHOULD MIRO BE STORED?

- Avoid poisoning! This medicine and any other medicine, must be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use **Miro** 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 the medicine at a temperature below 25°C and in a place protected from light.
- Do not discard medicines via the household wastewater or waste bin. Ask the pharmacist how to dispose of medicines that are no longer in use. These measures will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains inactive ingredients: Microcrystalline cellulose, Lactose (anhydrous), Sodium starch glycollate, Colloidal silicon dioxide, Magnesium stearate, Opadry OY-8704.

Each **Miro 30** tablet contains 60 mg lactose.
Each **Miro 45** tablet contains 90 mg lactose.

What the medicine looks like and the contents of the package:
Miro tablets are film-coated, round, biconvex, orange tablets with a score line on one side. The tablets come in packages of 10, 15, 20 or 30 tablets. They are packaged in trays (blister) inserted in a carton package.
Not all package sizes may be marketed.

Registration holder and address: Unipharm Ltd., P.O. Box 21429, Tel Aviv, 6121301.
Manufacturer and address: Unipharm Ltd., "Mevo Carmel" Industrial Park.
Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:
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Miro 45: 128 63 30739 02

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