Patient Package Insert in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed by a doctor's prescription only

ZYPADHERA 300 mg

Powder and solvent for preparation of prolonged release suspension for injection

Name and quantity of active ingredient:

Each vial of powder contains:

Olanzapine pamoate monohydrate equivalent to 300 mg Olanzapine

The reconstituted suspension contains:

Olanzapine 150 mg/ml

ZYPADHERA 405 mg

Powder and solvent for preparation of prolonged release suspension for injection

Each vial of powder contains:

Olanzapine pamoate monohydrate equivalent to 405 mg Olanzapine

The reconstituted suspension contains:

Olanzapine 150 mg/ml

For a list of the inactive ingredients, please see section 6.

Read this patient leaflet carefully in its entirety before using this medicine. This leaflet contains concise information regarding this medicine. If you have any further questions, please contact your doctor or pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not give this medication to others. it might harm them even if you think your illness is similar.

Very important information about this medicine:

Antipsychotics (like **ZypAdhera**) can increase the risk of death in elderly people who are experiencing confusion, memory loss, and loss of touch with reality (dementia associated with psychosis). This medicine is not intended for adult patients who suffer from psychosis related to dementia.

ZypAdhera is usually not intended for children and adolescents under the age of 18, since there is limited experience with this group.

This medicine is intended for adults who have previously been treated with olanzapine tablets.

1. WHAT IS THIS MEDICINE INTENDED FOR?

ZypAdhera is an antipsychotic preparation containing the active ingredient Olanzapine.
The preparation is administered as a prolonged release injection, for the treatment of schizophrenic patients.

Therapeutic group:
Atypical antipsychotic drugs.

2. BEFORE USING THIS MEDICINE:

This preparation should not be used if:

- You are sensitive to Olanzapine or to one of the other ingredients of the medicine. Signs of an allergic reaction include: rash, difficulty swallowing or breathing, swelling of the lips, face, throat, or tongue.
- You are breastfeeding.
- You suffer from or have the potential to develop narrow angle glaucoma.
- You suffer from dementia-related psychosis.
- Your condition is properly controlled with orally administered Zyprexa.

Special warnings pertaining to the use of this medicine:

- Avoid situations which may involve an excessive rise in body temperature and dehydration, such as increased physical activity or frequent stay in warm places.
- On the day of injection, you must remain under medical supervision at the medical center for at least 3 hours from the time of injection.
- In the event that **ZypAdhera** enters the bloodstream too quickly, the following symptoms may occur, which can lead to unconsciousness: excessive sleepiness, dizziness, confusion, disorientation, irritability, anxiety, aggression, increase in blood pressure, difficulty in talking and/or walking, weakness, muscle stiffness or shaking, convulsions. In most cases where these symptoms occurred, they appeared about one hour after injection. **Therefore, you must remain in the medical center for at least 3 hours from the time of injection, so that if necessary, you may receive immediate medical attention, or be brought to the Emergency Room. If you experience any of these symptoms you may be asked to wait longer at the medical center. Due to this risk, do not drive or operate machinery until the following day.**

These symptoms usually subsided 24 to 72 hours after the injection. In the event that one of these symptoms appears when you are no longer under the supervision of the medical staff, you must notify the doctor or nurse immediately.

- Tell the doctor or nurse if you feel dizzy after the injection. You must lie down until you feel better. The doctor or nurse may request to measure your blood pressure.
- The administration of ZypAdhera is not recommended in elderly patients suffering from dementia due to the possibility of severe side effects.
- In rare cases, medications of this type may cause involuntary movements, mainly of the face or tongue, or a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness. If you experience any of these symptoms, contact the doctor or nurse immediately.
- Weight gain was observed in patients taking ZypAdhera. Your weight should be monitored regularly. Contact a dietician for help with a diet plan if necessary.
- You should monitor blood glucose levels and lipids, as ZypAdhera may increase these measures. Let your doctor know if there is a family history of blood clots.

Before starting treatment with ZypAdhera tell the doctor if:

- You are sensitive to any food or drug.
- You suffer or have suffered in the past from impaired function of the heart (e.g.: heart attack, heart disease, abnormal heart rhythms, angina pectoris) and/or of the blood vessels (e.g.: if you or your family members suffer/have suffered from blood clots).
- You suffer or have suffered in the past from a stroke.
- You suffer from problems in the eyes (e.g. glaucoma, in particular narrow-angle glaucoma), the liver, the kidneys, the digestive system (e.g. intestinal obstruction), the blood system, the nervous system (Parkinson's disease), the bone marrow.
- You suffer or have suffered in the past from an enlarged prostate gland.
- You suffer from epilepsy, diabetes, low blood pressure, high cholesterol or triglyceride levels in the blood.
- If you are over the age of 65, the doctor might monitor your blood pressure values.
- If you are over the age of 75 – it is not recommended to start treatment with ZypAdhera due to the physiological body changes and reduced muscle mass.

If you are taking other drugs concomitantly, including non-prescription medicines or nutritional supplements, inform the doctor or pharmacist. It is especially important to notify the doctor or pharmacist if you are taking:

- Drugs affecting CYP1A2 such as Fluvoxamine (an antidepressant), Ciprofloxacin (an antibiotic) or Carbamazepine (an antiepileptic and mood stabilizer) - there might be a need to adjust the dosage of **ZypAdhera**.
- Drugs affecting the central nervous system such as: tranquillizers, sedatives or antidepressants - concomitant use may cause drowsiness.
- Drugs for Parkinson's - concomitant use may exacerbate the symptoms of Parkinson's disease.
- Antiepileptic drugs - proceed with caution when administering to patients with a history of epilepsy or patients taking drugs which lower the seizure threshold.
- Drugs known to affect the electrical conduction in the heart (prolong the QT interval) - proceed with caution when administering the combination of **ZypAdhera** and drugs that affect the electrical conduction in the heart.

Drug use and alcohol consumption:

Avoid consumption of alcoholic beverages during treatment with this drug, as it may increase drowsiness.

Pregnancy and breastfeeding:

Consult the doctor or pharmacist before using medications.

Consult the doctor if you are pregnant or plan to become pregnant. Newborns may develop a withdrawal syndrome if the mother took the drug during the last trimester (last three months) of pregnancy. The withdrawal syndrome includes the following symptoms: tremor, muscle rigidity/weakness, drowsiness, irritability, breathing problems and difficulty in feeding. If your baby develops one or more of the above symptoms, contact the doctor.

This drug should not be taken if you are breastfeeding. A small amount of the drug may cross into the milk.

Driving and using machines:

Use of this medicine may impair alertness and therefore caution should be exercised when driving a car, operating dangerous machinery and in any other activity that requires alertness. Do not drive or operate machinery on the day of injection.

Smoking:
If you are a smoker, inform the doctor before commencing treatment with this medicine.

3. HOW TO USE THIS MEDICINE?

Always use according to the doctor's instructions. If you are unsure, check with the doctor or pharmacist.

The dosage and manner of treatment will be determined only by the doctor. The recommended dosage is usually:
A **ZypAdhera** injection contains Olanzapine for prolonged release, injection frequency will be once in two or four weeks according to the doctor's instructions.

Directions for use:

- **ZypAdhera** is to be administered only by a trained doctor or nurse in an authorized medical center with immediate access to emergency and resuscitation services.
- The injection is administered to the gluteal muscle.
- Detailed instructions for preparation and injection are included in the prescribing information enclosed in the package.
- After the injection, you must remain at the medical center for at least 3 hours.

Treatment should be continued as recommended by the doctor.
If you accidently received an overdose:
This medicine is administered by medical staff, so an overdose is unlikely.
Patients who have received an overdose have experienced the following symptoms:
Rapid heart rate, agitation/aggressiveness, speech problems, involuntary movements (especially of the face or tongue) and a reduced level of consciousness. Other symptoms may include:
Acute confusion, epileptic seizures, coma, combination of fever, faster breathing, sweating, muscle stiffness and drowsiness, slow breathing, aspiration, low or high blood pressure, abnormal rhythms of the heart.

If you experience any of the above symptoms, contact your doctor or go immediately to the hospital Emergency Room.

If you forget to come and get the injection of this drug on the required date, contact the doctor as soon as possible to schedule a new date.

Examinations and follow-up:

- During treatment with this medicine, you must be under medical supervision and monitor your blood pressure, especially if you are over the age of 65.
- You should monitor blood glucose levels at the beginning and during treatment, especially if you suffer from diabetes or borderline glucose levels (fasting glucose levels of 100-126 mg/dL) and blood lipid levels, especially in patients suffering from disturbances in blood lipid levels or with the risk factors of developing such disturbances.
- Body weight should be monitored during treatment.

If you stop taking this medicine

Even if there is an improvement in your health, do not stop taking this medicine without consulting the doctor.

Side effects such as: sweating, insomnia, tremor, anxiety, nausea or vomiting, were rarely reported in patients who abruptly discontinued the oral treatment with Olanzapine.

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

4. SIDE EFFECTS:

Like every medicine, the use of **ZypAdhera** may cause side effects in some users. Do not be alarmed when you read the list of side effects. You may not suffer from any of them.

Notify the doctor or nurse immediately if:

- After the injection you feel: excessive sleepiness, dizziness, confusion, disorientation, difficulty walking or talking, muscle stiffness or shaking, weakness, irritability, anxiety, aggression, increase in blood pressure or convulsions that can lead to unconsciousness. These symptoms may occur when **ZypAdhera** enters the bloodstream too quickly.

- After the injection you experience the following symptoms: high fever, muscle rigidity, altered mental status, unstable heart rate and blood pressure, tachycardia, excessive sweating. These symptoms are expressions of a very rare side effect of antipsychotic medicines, called Neuroleptic Malignant Syndrome.
- After the injection you experience the following rare symptoms: involuntary movements, especially of the face or tongue. These symptoms are expressions of another side effect characteristic of antipsychotic drugs, called Tardive Dyskinesia. In this case, the drug dosage is to be decreased or the treatment should be discontinued.
- You have symptoms indicating vein thrombosis: swelling, pain and redness in the legs that may be accompanied by chest pain and difficulty breathing.

Side effects related to treatment with ZypAdhera:

Sleepiness and pain at the injection site – frequent.

Infection at the injection site - uncommon.

- **When body temperature is likely to increase, for example during physical activity or staying in hot places, signs of dehydration may appear, such as:** fever, excessive sweating or lack of sweating, dry mouth, excessive thirst, urinary retention.

Side effects related to oral treatment with Olanzapine tablets that can also appear with ZypAdhera:

Common side effects: weight gain, elevation of blood prolactin levels, dry mouth, constipation, tremor, restlessness, increased appetite, dizziness, involuntary movements, exhaustion, extreme fatigue, fluid retention (that causes swelling of the hands, ankles or feet), fever, joint pain, sexual dysfunctions (loss of sexual desire, erectile dysfunctions), changes in levels of blood cells, circulating fats and in early stages of the treatment also an increase in hepatic enzymes, increase in blood and urine glucose levels, increase of uric acid and creatine phosphokinase levels in the blood, rash.

At the beginning of treatment, some patients experience dizziness, especially when standing up from a sitting or lying position. This side effect usually disappears on its own. You must sit or lie down until you feel improvement. If there is no improvement, consult the doctor.

Uncommon side effects: hypersensitivity (swelling in the mouth and throat, itching, rash), diabetes or worsening of existing diabetes, occasionally associated with ketones in the blood and urine (ketoacidosis) or coma, seizures; usually associated with a history of epilepsy, muscle stiffness or spasms (including eye movements), restless legs syndrome, speech problems, slow

heart rate, sensitivity to sunlight, nose bleeds, memory impairment, abdominal bloating, urinary incontinence, urinary retention, hair loss, absence or decrease in menstrual periods, changes in breasts in males and females (such as an abnormal production of breast milk or abnormal growth).

Rare side effects: decrease in body temperature, abnormal rhythms of the heart, sudden death, pancreatitis that causes severe stomach pain, fever and sickness, liver disease (jaundice of the skin and sclera of the eyes), muscle injury that causes unexplained muscle aches, prolonged/painful erections.

Side effects of unknown frequency: Severe allergic reactions such as eosinophilia and systemic symptoms (Drug Reaction with Eosinophilia and Systemic Symptoms - DRESS). This side effect begins with flu-like symptom with a rash on the face and then an extended rash, high fever, enlarged lymph nodes, elevated levels of liver enzymes, and elevated levels of a certain type of white blood cell (eosinophilia).

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

Reporting side effects

Side effects can be reported to the Ministry of Health via an online form for reporting side effects in the Ministry of Health's website www.health.gov.il or by entering the following link: https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. HOW TO STORE THIS MEDICINE?

- Avoid poisoning! To avoid poisoning, this medicine and all other medicines must be stored in a secured place out of the reach of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medication after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
- Store at room temperature, below 30^0C.
- Do not refrigerate or freeze.
- The medicine should be used immediately after preparation.

6. ADDITIONAL INFORMATION

Apart from the active ingredient, the medication also contains:

The powder does not contain additional ingredients.

The solvent contains:

Carmellose sodium, mannitol, polysorbate 80, water for injections, hydrochloric acid and sodium hydroxide.

How the drug looks like and the contents of the package:

A vial with dry powder, a vial with solvent, a syringe with an attached needle and three separate needles. The needles are protected with a safety cap.

License holder: Eli Lilly Israel Ltd., P.O Box 2160, Herzliya Pituach 4672511.

Manufacturer: Lilly S.A., Alcobendas, Madrid, Spain

Drug registration number in the National Drug Registry in the Ministry of Health:

ZypAdhera 300 mg: 145-02-31988-02

ZypAdhera 405 mg: 145-03-31989-02

This leaflet was reviewed and approved by the Ministry of Health in June 2017.

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