SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fenazepam Olainfarm 0.5 mg tablets
Fenazepam Olainfarm 1 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION OF THE PRODUCT

*Active substance:* Fenazepam (Fenazepamum).

- Each Fenazepam Olainfarm 0.5 mg tablet contains 0.5 mg of fenazepam.
- Each Fenazepam Olainfarm 0.5 mg tablet contains 83.50 mg of lactose monohydrate.
- For the full list of excipients see section 6.1
- Each Fenazepam Olainfarm 1 mg tablet contains 1 mg of fenazepam.
- Each Fenazepam Olainfarm 1 mg tablet contains 125 mg of lactose monohydrate.
- For the full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Tablets.
*Description:* White or almost white, round flat tablets with beveled edge.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Anxiety, fear, psychomotor agitation, vegetative disorders and psychotic states; neuroses and neurosis-like states; psychopathy, and psychopathy-like conditions, insomnia, increased muscle tone, hyperkinesia, epilepsy, complex treatment of alcohol abstinence syndrome.

4.2 Posology and method of administration

Fenazepam tablets are taken orally with liquid. It is recommended to use the lowest effective dose for the possible shortest time.

*Anxiety, fear, psychomotor agitation, vegetative disorders, psychotic state:* adults are usually administered a single dose of 0.5 mg to 1 mg, the mean daily dose is 1.5 mg to 5 mg divided into 2-3 single doses (usually in the morning and the afternoon - 0.5 mg to 1 mg, at bedtime - up to 2.5 mg).

*Neuroses and neurosis-like states, psychopathy, psychopathy-like conditions:* initial dose - 0.5 mg to 1 mg 2-3 times a day. If necessary, after 2-3 days the dose may be increased to 4-6 mg daily. In case of extreme agitation an initial dose is 3 mg a day, and then the dose is increased rapidly to reach the therapeutic effect.

The maximum daily dose should not exceed 10 mg.

*Insomnia:* 0.25 mg - 0.5 mg 20-30 minutes before bedtime.
Summary of Product Characteristics

1. Increased muscle tonus: 2-3 mg 1-2 times a day.

2. Epilepsy: 2-10 mg per day.

3. Alcohol abstinence syndrome complex treatment: 2.5-5 mg daily.

4. Elderly patients: daily dose is reduced 2-3 times.

5. Patients with hepatic and/or renal failure: the dose is reduced.

6. Children under the age of 18: Fenazepam Olainfarm must not be used (see section 4.4).

**Duration of administration**

In order to avoid dependence Fenazepam like other benzodiazepines is usually recommended to use for the shortest possible period starting from several days till 4 days maximum including the period of dose reducing.

Discontinuation is done gradually reducing the dose. Abrupt discontinuation may cause withdrawal symptoms: irritability, anxiety, sleep disturbances.

### 4.3 Contraindications

Hypersensitivity to benzodiazepine derivatives or excipients of the preparation.

Myasthenia gravis.

Heavily compromised liver and kidney functions.

Severe respiratory disease (respiratory failure, acute pulmonary insufficiency, sleep apnea syndrome).

Acute front closed-angle glaucoma.

Severe depression.

Asthenia. Cachexia.

Pregnancy and breast-feeding.

Children and adolescents under 18 years of age.

Acute poisoning with alcohol, tranquilizers, neuroleptics, hypnotics, narcotics.

Drinking alcohol during treatment.

Not recommended for asthma sufferers and the elderly.

### 4.4 Special warnings and special precautions for use

Prescribing Fenazepam the general information on benzodiazepines should be taken into account.
Fenazepam should not be used in children under 18 years of age due to lack of data on safety and efficacy in this age group.

**Tolerance**

Prolonged use of Fenazepam Olainfarm causes the gradual weakening of the medicine’s effect, which may cause the patient’s arbitrarily increasing the dose to achieve the desired effect.

**Dependence**

Should be prescribed with caution in patients with a history of medicines, drugs or alcohol addiction. Patients, who have not previously been treated with psychotropic drugs, should require lower dose of Fenazepam Olainfarm compared to patients, who have already been treated with antidepressants, anxiolytics, as well as to patients with alcohol dependence.

Increase of dosage and treatment duration promotes dependence. If you need a dose increase, it should be done slowly. Administration of Fenazepam Olainfarm for several weeks at doses higher than 4 mg a day can develop physical and psychic dependence. Patients who have had an addiction to alcohol or other drugs have greater risk of addiction.

Medicine rapid cessation after the prolonged use causes withdrawal symptoms: irritability, anxiety, sleep disturbances. To avoid withdrawal symptoms Fenazepam Olainfarm is discontinued gradually by reducing the dose.

Individual patients may experience withdrawal symptoms even after short-term administration, especially when used in high doses.

**Paradoxical reactions**

Benzodiazepines including Fenazepam Olainfarm can cause paradoxical reactions. They can be expressed as anxiety, irritability, anger, aggression, hallucinations, nightmares, insomnia, inappropriate behavior and other adverse behavioral effects. They occur most likely in the elderly and mentally ill patients, as well as after a single use of alcohol. In case of occurrence of paradoxical reactions treatment with Fenazepam Olainfarm should be stopped immediately.

**Special patient group**

*Patients with cerebral and spinal ataxia* - Fenazepam Olainfarm should be indicated with caution.

*Patients with mental illnesses, as well as with organic brain changes,* there may have paradoxical reactions. Monotherapy with these medicines may increase suicidal ideation.
Summary of Product Characteristics

Patients with asthma and elderly patients - Fenazepam Olainfarm can worsen patency of airways. Elderly patients - the dose should be reduced because risk of adverse reactions is increased. Coordination and balance disorders with muscle weakness may lead to falls and injuries. In patients with hepatic and / or renal failure, the active substance can accumulate in the body, enhancing medicines and side effects. During the long-term use of the preparation periodic blood counts and liver function tests should be performed. During treatment with Fenazepam Olainfarm prescribing the other drugs should be done with caution due to possible interactions (see section 4.5).

Excipients

- Each Fenazepam Olainfarm 0.5 mg tablet contains 83.50 mg of lactose monohydrate.
- Each Fenazepam Olainfarm 1 mg tablet contains 125 mg of lactose monohydrate.

This drug should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

4.4 Interaction with other medicinal products and other forms of interaction

Using concomitantly Fenazepam and other central nervous system depressant drugs (neuroleptics, anti-epileptic drugs, hypnotics, centrally acting muscle relaxants, narcotic analgesics), it is necessary to take into account that complex administration of medicines increases their effect.

Cytochrome P450 inhibitors (e.g. cimetidine) increases Fenazepam activity and the risk of toxic effects.

Cytochrome P450 inducers (e.g. rifampicin) decreases Fenazepam activity.

Fenazepam increases tricyclic antidepressant imipramine concentration in blood plasma and sedative effect.

Concomitant use of Fenazepam with antihypertensive medicinal products may enhance the activity of these resources.

Benzodiazepines including Fenazepam weaken Parkinson activity of levodopa, may increase parkinsonian symptoms.

Concomitant use of Fenazepam with zidovudine increases toxicity of zidovudine.
Concomitant use with clozapine may increase risk of respiratory inhibition.

Oral contraceptives decrease Fenazepam metabolism.

Smoking decreases Fenazepam effect.

Alcohol should not be used during treatment (can cause life-threatening condition - respiratory centre paralysis).

4.5 Pregnancy and lactation

Use of benzodiazepine derivatives including Fenazepam during pregnancy is contraindicated.

Fenazepam has a toxic effect on the foetus. Its use during the first three months of pregnancy increases foetal risk of congenital malformations, the use of Fenazepam during the last months before birth or in the newborn may cause central nervous system depression, addiction and withdrawal symptoms.

Newborn infants are particularly sensitive to central nervous system depression caused by benzodiazepines, which can result in respiratory depression, low muscle tone and blood pressure, transient hypothermia, sucking weakness ("flabby child" syndrome).

Fenazepam excreted in breast milk, therefore it is necessary to discontinue the medicine use during breast-feeding, or breast-feeding itself.

4.7 Effects on ability to drive and use machines

During administration of Fenazepam it is not allowed to drive or operate potentially dangerous machinery, because the drug reduces attention, response speed and precision of movement.

4.8 Undesirable effects

Side effects are mainly dependent on the dose and different patients may have various side effects.

Classification of side effects frequency:

Very common: affect more than 1 in 10 treated patients (≥ 1/10);

Common: affect less than 1 in 10, but more than 1 in 100 treated patients (≥ 1/100 to < 1/10);

Uncommon: affect less than 1 in 100, but more than 1 in 1,000 treated patients (≥ 1/1000 to < 1/100);

Rare: affect less than 1 in 1,000 but more than 1 in 10,000 treated patients (≥ 1/10 000 to < 1/1000);

Very rare: affect less than 1 in 10,000 treated patients including some case reports (< 1/10 000);

Not known (cannot be estimated from available data).
Adverse effects caused by Fenazepam depend on a patient’s individual sensitivity, dose and speed of dose increase. If a dose is increased slowly and it is not more than 1.5-2.5 mg a day, adverse effects are actually not observed. If a dose is increased rapidly and it is more than 5-7 mg a day, frequency of adverse effects is increased. Undesirable effects are decreased or disappear when a dose is reduced.

**Blood and lymphatic system disorders:** rare - blood disorders (leukopenia, neutropenia, anemia, thrombocytopenia).

**Psychiatric disorders:** uncommon - disorientation in time and space, very rare - paradoxical reactions (extreme restlessness, irritability, anger, aggression, hallucinations, nightmares, insomnia, inappropriate behaviour and other adverse behavioural effects), thoughts of suicide. Usually paradoxical reactions have been observed in the elderly and mentally ill patients, as well as simultaneous medicines and alcohol use. In such cases, the medicine should be discontinued immediately.

**Nervous system disorders:** common - drowsiness, mild headache, muscle weakness, gait and balance disorders (particularly in patients older than 65 years), attention and concentration reduction, uncommon - dizziness, slurred speech, memory impairment. If reactions are severe, due to reducing the dose they weaken or disappear.

**Eye disorders:** vision (wide pupils, diplopia, blurred vision).

**Vascular disorders:** rare - a negligible hypotension.

**Gastrointestinal disorders:** rare - dry mouth, nausea, diarrhea.

**Liver and/or biliary system disorders:** rare - liver problems with jaundice.

**Skin and subcutaneous tissue disorders:** rare - skin rash, itching.

**Renal and urinary disorders:** common - problems with urination (urinary incontinence or urinary retention).

**Reproductive system and breast disorders:** uncommon - menstrual disorders, libido decrease.

During treatment there may occur undiagnosed condition before depression.

Administration of Fenazepam can lead to tolerance, physical and psychological dependence. Patients, who suffer from alcoholism or drug addiction, are particularly predisposed to the risk of addiction.

### 4.9 Overdose

**Symptoms:** expressed central nervous system depression (drowsiness, confusion, slurred speech and vision, coordination and balance problems), breathing difficulty, hypotension (dizziness, heart rate).

**Procedures:** reduce drug absorption using activated charcoal (optimal - the first hour after ingestion).
Treatment is symptomatic – monitoring and maintenance of the major life functions: the upper airway and breathing (if necessary, pulmonary ventilation), provision of hemodynamics. Flumazenil is effective in case of benzodiazepine-induced respiratory depression. Hemodialysis is not effective.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** anxiolitics (benzodiazepine derivatives).

**ATC code:** N05B A.

Fenazepam is anxiolytic agent with an expressed anxiolytic, anticonvulsant, muscle relaxant, hypnotic, and sedative effect.

Anxiolytic activity manifested as anxiety, fear, anxiety and emotional arousal reducing or inhibition; anticonvulsant activity – reducing frequency of epileptic seizures; myorelaxing action - skeletal muscles relaxation, sleep effect – sleep normalization, and the prolongation of sleep in case of insomnia caused by anxiety, sedative action – reducing the psychomotor agitation, while at the same time attenuation in concentration and reaction rate. Fenazepam can also be used to treat psychosis in a combination with antipsychotics.

The mechanism of action is not fully studied. It is considered that tranquilizers prevent subcortical centre (thalamus and the limbic system) agitation, as well as polysynaptic spinal reflexes that cause myorelaxation. Benzodiazepines implement their effects on subcortical centers by binding to specific benzodiazepine receptors, increasing gamma-amino-butyric acid (GABA) ergic processes and thereby producing a calming effect.

Fenazepam has therapeutic effect in case of chronic alcohol intoxication that expresses in the full or partial normalization of enzyme system activity changed because of the use of ethanol.

5.2 Pharmacokinetic properties

Fenazepam is quickly and fully absorbed from the digestive tract. Maximum concentration of the active substance is reached in 1-2 hours after intake. After a single oral dose of 2 mg maximum blood concentration is 8-15 ng / ml, after oral repeated doses balanced concentration is reached in 10-14 days. Fenazepam penetrates well into body tissues and readily crosses the blood-brain and placental barrier and is excreted in breast milk. Fenazepam biotransformation occurs primarily in the liver by oxidation and conjugation with glucuronic acid, creating a pharmacologically active
metabolite 3-hydroxy-phenazepam and several inactive metabolites. Elimination half-life is 6-18 hours. The great part of the dose is excreted from the body in the urine as metabolites. Only a small amount of the dose is excreted unchanged.

After repeated administration the drug accumulation is not observed. In case of liver and kidney failure hepatic and renal clearance are reduced, which can lead to accumulation. Also, elderly patients have a greater occurrence of accumulation and risk of side effects.

5.3 Preclinical safety data

Acute toxicity: oral LD_{50} in mice – 2400 mg / kg, in rats intraperitoneally LD_{50}− 720 mg / kg. There are no clinical data that benzodiazepine derivatives have carcinogenic activity. Teratogenicity and embryotoxicity. Research has shown an increased fetal damage and risk of offspring behavioral change caused by benzodiazepines.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

- Fenazepam 0.5 mg tablets: 83.50 mg of lactose monohydrate, corn starch, silicon dioxide, magnesium stearate
- Fenazepam 1 mg tablets: 125.0 mg of lactose monohydrate, corn starch, silicon dioxide, magnesium stearate.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage:

Do not store above 25 °C. Protect from light and moisture.

6.5 Nature and contents of container

- 10 tablets in blister from transparent PVC film and aluminium foil
- 5 blisters (50 tablets) with package leaflet in the carton pack.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.
7. MARKETING AUTHORISATION HOLDER
JSC “Olainfarm”
Address: 5 Rupnicu St., Olaine, LV-2114, Latvia.
Phone: +371 67013701; fax: +371 67013777; e-mail: olainfarm@olainfarm.lv

8. MARKETING AUTHORISATION NUMBER
• Fenazepam Olainfarm 0.5 mg tablets – 99-0882;
• Fenazepam Olainfarm 1 mg tablets – 99-0883.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
15.12.1999. / 13.04.2005 (Fenazepam 0.5 mg tablets and Fenazepam 1 mg tablets);
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10. DATE OF REVISION OF THE TEXT:
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