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

Subutex 2 mg
Sublingual tablets

Subutex 8 mg
Sublingual tablets

Active ingredients:
Each Subutex 2 mg tablet contains: Buprenorphine (as hydrochloride) 2 mg
Each Subutex 8 mg tablet contains: Buprenorphine (as hydrochloride) 8 mg

Inactive ingredients and allergens: see section 6 "Further Information" and in section 2 "Important information regarding some of the ingredients of the medicine".

Read this leaflet carefully in its entirety before using the medicine.
This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
This medicine has been prescribed to treat your ailment. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.
The medicine is intended for use in adults and adolescents over 16 years of age.

1. WHAT IS THE MEDICINE INTENDED FOR?
Subutex is used to treat people addicted to opioid drugs (narcotics), such as morphine and heroin, who have agreed to be treated for their addiction. Subutex is intended for use in adults and adolescents over the age of 16 who are also receiving medical, social and psychological support.

Therapeutic group:
Buprenorphine - semi-synthetic opioid.

2. BEFORE USING THE MEDICINE
2.1 Do not use the medicine if:

- You are allergic (hypersensitive) to buprenorphine or any of the other ingredients in this medicine (see section 6).
- You are breastfeeding.
- You have **serious breathing problems**.
- You have **serious problems with your liver**.
- You are a child under the age of 16 years.
- You suffer from intoxication due to alcohol consumption or if you suffer from trembling, sweating, confusion, anxiety, or hallucinations caused by alcohol.

2.2 Special warnings regarding use of the medicine

- **Misuse, abuse and diversion**
  This medicine can be a target for people who abuse prescription medicines, and should be kept in a safe place to protect it from theft. Opioids should only be used by those they are prescribed for. **Do not give your medicine to anyone else**. Taking higher doses or more frequent doses of opioid may increase the risk of addiction. Overuse and misuse can lead to overdose and/or death.

- **Breathing problems**
  Some people have died from respiratory failure (inability to breathe) because they misused this medicine or took it in combination with other central nervous system depressants, such as alcohol, benzodiazepines (tranquilizers) or other opioids.

- **Addiction and withdrawal symptoms**
  Taking this medicine regularly, particularly for a long time, can lead to addiction.

  Addiction can cause withdrawal symptoms when you stop taking this medicine. Withdrawal symptoms can include restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, loss of appetite, trembling, shivering or sweating. Your doctor will discuss with you how to gradually reduce your dose before stopping the medicine. It is important that you do not stop taking the medicine suddenly as you will be more likely to experience withdrawal symptoms.

  This product can cause withdrawal symptoms if you take it less than 6 hours after you use a short-acting opioid (e.g. morphine, heroin) or less than 24 hours after you use a long-acting opioid, such as methadone.

- **Liver damage**
  Liver damage has been reported after taking Subutex, especially when the medicine is misused. This could also be due to viral infections (chronic hepatitis C), alcohol abuse, anorexia or use of other medicines with the ability to harm your liver (see section 4 “Side effects”). **Your doctor may instruct you to have routine blood tests performed to monitor the condition of your liver. Before starting treatment with Subutex, inform the doctor if you have liver problems.**

- **Blood pressure**
  This medicine may cause a sudden drop in your blood pressure, causing you to feel dizzy if you get up too quickly from sitting or lying down.

- **Diagnosis of unrelated medical conditions**
  This medicine may mask pain symptoms that could assist in the diagnosis of some diseases. Do not forget to inform your doctor that you are taking this medicine.

Before treatment with Subutex, tell the doctor if:
- You have seizures, fits or convulsions.
- You have asthma or other breathing problems.
- You have any liver disease such as hepatitis.
- You have low blood pressure.
- You have recently suffered head injury or brain disease.
- You have any kidney disease.
- You have urinary disorder (especially linked to enlarged prostate in men).
- You have thyroid problems.
- You have endocrine system disruption (such as Addison's disease).
- You have depression or other conditions that are treated with antidepressants. The use of these medicines together with Subutex can lead to serotonin syndrome, a potentially life-threatening condition (see below “Drug interactions”).

2.3 Children and adolescents
The medicine is not intended for use in children and adolescents under 16 years of age.

2.4 Drug interactions/reactions:
If you are taking, or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist.
Some medicines may increase the side effects of Subutex and may sometimes cause very serious reactions. Do not take other medicines whilst taking Subutex without first talking to your doctor.
In particular, inform the doctor or pharmacist if you are taking:
- **Benzodiazepines** (used to treat anxiety or sleep disorders) such as diazepam, temazepam, alprazolam. Concomitant use of Subutex and sedative medicines such as benzodiazepines or related drugs increases the risk of drowsiness, difficulties in breathing (respiratory depression), coma and may be life-threatening. Because of this, concomitant use should only be considered when other treatment options are not possible. However if your doctor does prescribe Subutex together with sedative medicines the dose and duration of concomitant treatment should be limited by your doctor. Please tell your doctor about all sedative medicines you are taking, and follow your doctor’s dose recommendation

closely. It could be helpful to inform friends or relatives to be aware of the signs and symptoms stated above. Contact your doctor when experiencing such symptoms.

- **Anti-depressants**, such as moclobemide, tranylcypromine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepine, or trimipramine. These medicines may interact with Subutex and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, hallucinations, coma, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C. Contact your doctor when experiencing such symptoms.
- **Other medicines that may make you feel sleepy** which are used to treat illnesses, such as anxiety, sleeplessness, convulsions/seizures, pain. These types of medicines will reduce your alertness levels making it difficult for you to drive or operate machines. They may also cause central nervous system depression, which is very serious. Below is a list of examples of these types of medicines:
  - other opioid containing medicines, such as methadone, certain pain killers and cough suppressants.
  - antidepressants (used to treat depression) such as isocarboxazid, phenelzine, selegiline, tranylcypromine, and valproate may increase the effects of this medicine.
  - sedative H_1 receptor antagonists (used to treat allergic reactions) such as diphenhydramine and chlorphenamine.
  - barbiturates (used to cause sleep or sedation) such as phenobarbital, secobarbital.
  - tranquilizers (used to cause sleep or sedation) such as chloral hydrate.
- Naltrexone may prevent Subutex from working. If you take naltrexone whilst you are taking Subutex, you may experience a sudden onset of prolonged and intense withdrawal symptoms.
- Clonidine (used to treat high blood pressure) may extend the effects of this medicine.
- Anti-retroviral medicines (used to treat AIDS) such as ritonavir, nelfinavir, indinavir, may increase the effects of this medicine.
- Some antifungal medicines (used to treat fungal infections) such as ketoconazole and itraconazole and certain antibiotics (macrolides), may extend the effects of this medicine.
- Some medicines may decrease the effect of Subutex. These include medicines used to treat epilepsy (such as carbamazepine and phenytoin) and medicines used to treat tuberculosis (rifampicin).

To get the greatest benefit from taking Subutex, you must tell your doctor about all the medicines you are taking, including alcohol, medicines containing alcohol, street drugs and any prescription medicine you are taking that has not been prescribed for you by your doctor.

2.5 Use of the medicine with food, drink and alcohol

Alcohol may increase drowsiness and may increase the risk of respiratory failure (inability to breathe) if taken with Subutex.

Do not take Subutex together with alcohol.

Do not swallow or consume food or drink until the tablet is completely dissolved.

2.6 Pregnancy, breastfeeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take Subutex if you are pregnant or think you might be pregnant unless you have discussed this with your doctor and the benefits of treatment are considered to outweigh the potential harm to the baby.

If you use Subutex during the last 3 months of pregnancy, your baby may become dependent and experience withdrawal symptoms, including problems with breathing after the birth which may need to be treated. These symptoms may occur up to several days after birth.

Do not take Subutex while you are breastfeeding, as buprenorphine passes into breast milk and will affect your baby.

2.7 Driving and operating machinery

If you feel drowsy or dizzy while taking this medicine, do not operate machinery.

This medicine can affect your ability to drive, since it may make you sleepy or dizzy.

Do not drive while taking this medicine until you know how it affects you.

Talk to your doctor or pharmacist if you are unsure whether it is safe for you to drive while taking this medicine.

2.8 Important information about some of the ingredients in the medicine

Subutex contains lactose and sodium. If you have been told by your doctor that you have an intolerance

to certain sugars, inform your doctor before taking this medicine.
Each Subutex 2 mg tablet contains approximately 48 mg lactose monohydrate.
Each Subutex 8 mg tablet contains approximately 192 mg lactose monohydrate.
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. HOW SHOULD YOU USE THE MEDICINE?

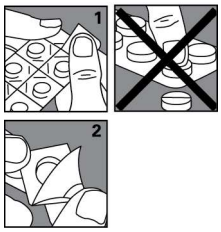
- Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain.
- The dosage and treatment regimen will be determined by the doctor only.
- **Do not exceed the recommended dose.**
- To avoid sudden withdrawal symptoms, start treatment with Subutex when there are already clear signs of withdrawal.

- During treatment, the doctor may increase the Subutex dose to a maximum daily dosage of 32 mg, depending on your response. Once you have been stable for a while, the doctor will gradually reduce the dosage and it may be possible to stop it altogether.
- Do not suddenly stop taking the medicine, as this may cause withdrawal symptoms.

How to use

- Place the tablet under your tongue and allow it to dissolve. This may take 5-10 minutes.
- This is the only way to take the tablet. Do not divide, chew or crush the tablet, because the medicine will not work and you may suffer from withdrawal symptoms.
- While Subutex dissolves, do not chew or swallow the tablets whole, because they will not have an effect.

How to remove the tablet from the blister pack:



1 - Remove just one section from the blister pack, by tearing it along the perforated line.
2 - Starting from the edge where the seal is lifted, pull back the aluminum foil to remove the tablet.

If you accidentally take too high a dosage

- If you took an overdose, or if a child has accidentally swallowed the medicine, proceed immediately to a hospital emergency room and bring the package of the medicine with you, since an overdose of Subutex may cause severe and life-threatening breathing problems.

If you forget to take the medicine

- Contact the doctor as soon as possible and follow his or her instructions.
- Do not take a double dose to compensate for a forgotten dose.

If you stop using the medicine

- Do not change or stop the treatment in any way without the agreement of your attending doctor. **Sudden discontinuation of treatment may cause withdrawal symptoms.**

- Adhere to the treatment regimen recommended by the doctor.
- Do not take medicines in the dark! Check the label and the dose <u>each time</u> 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, the use of Subutex may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Refer to the doctor immediately or seek urgent medical attention if you experience any of the following side effects:

- sudden wheezing, difficulty breathing, swelling of the eyelids, face, tongue, lips, throat or hands; rash or itching especially those covering your whole body. These may be signs of a life-threatening allergic reaction.

- if you start to breathe more slowly or weakly than expected (respiratory depression).
- if you feel you are about to faint, as this may be a sign of low blood pressure.

Also tell your doctor immediately if you experience any of the following side effects:
Severe fatigue, lack of appetite or if your skin or eyes look yellow. These may be symptoms of liver damage.

Additional side effects

Very common side effects *(may affect more than 1 in 10 users):*
Drug withdrawal syndrome, headache, sweating (hyperhidrosis), insomnia (inability to sleep), nausea, pain.
Common side effects *(may affect up to 1 in 10 users):*
Abdominal pain, agitation, anxiety, joint pain, weakness, back pain, bone pain, bronchitis, chest pain, chills, constipation, cough, decreased appetite, depression, diarrhea, dizziness, dry mouth, painful period, indigestion, shortness of breath, flatulence, gastrointestinal disorder, hostility, increase in muscle tension, infection, influenza, nervousness, tearing (watery eyes) disorder, swollen glands (lymph nodes), malaise, migraine, muscle spasms, muscle pain, dilation of the pupils, muscle pain, neck pain, palpitations, paranoia, burning or tingling in hands and feet, swelling (hands and feet), runny or stuffy nose, sore throat and painful swallowing, fever, rash, somnolence, syncope (fainting), abnormal thinking, tooth disorder, tremor; flushing, vomiting, yawning.
Side effects of unknown frequency *(frequency cannot be estimated from the available data):*
Drug dependence and addiction, seizures, drug withdrawal syndrome in newborn, hallucinations (sensing things that are not real), drop in blood pressure on changing position from sitting or lying down to standing, difficulty in passing urine, vertigo. Misusing this medicine by injecting it can cause withdrawal symptoms, infections, other skin reactions and potentially serious liver problems.

Drug Withdrawal
When you stop taking Subutex, you may experience drug withdrawal symptoms, which include restlessness, difficulty sleeping, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, feeling or being sick, diarrhoea, trembling, shivering or sweating.

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in the leaflet, consult the doctor.

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/

5. HOW SHOULD THE MEDICINE BE STORED?
- Avoid poisoning! This medicine and any other medicine should be kept in a safe place out of the reach and sight of other family members, 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 Subutex 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 below 30°C.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. FURTHER INFORMATION
- In addition to the active ingredient, the medicine also contains:
  Lactose monohydrate, Mannitol, Maize Starch, Povidone K30, Citric acid anhydrous, Magnesium stearate, Sodium citrate.
- **What Subutex tablets look like and the contents of the package**
  Subutex 2 mg sublingual tablets are oval, white, 10 mm x 5 mm in size, with “B2” debossed on one

side.
Subutex 8 mg sublingual tablets are oval, white, 14 mm x 7 mm in size, with “B8” debossed on one side.
The tablets are packaged in packs of 7 and 28 tablets.
Not all pack sizes are marketed.

Manufacturer and address: Indivior UK Limited, Hull, UK.
License holder and address: Naomi Shaco-Ezra Ltd., P.O.B 6825, Ramat Gan 52167.

Revised in December 2020.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Subutex 2 mg: 133 88 29872
Subutex 8 mg: 133 87 29873