PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Butrans 5, Butrans 10, Butrans 15, Butrans 20

Transdermal matrix patches

Active ingredient:

Each **Butrans 5** transdermal patch contains: buprenorphine 5 mg, and releases 5 mcg per hour.
Each **Butrans 10** transdermal patch contains: buprenorphine 10 mg, and releases 10 mcg per hour.
Each **Butrans 15** transdermal patch contains: buprenorphine 15 mg, and releases 15 mcg per hour.
Each **Butrans 20** transdermal patch contains: buprenorphine 20 mg, and releases 20 mcg per hour.
For the list of the additional ingredients see section 6.

- **The patches contain a strong analgesic (opioid).**
- **Ensure that the old patches are removed before applying a new patch.**
- **Do not cut the patches.**
- **Do not expose the patches to a heat source (such as a hot water bottle).**
- **Do not take a hot shower or soak in a hot bath while the patch is affixed to the body.**
- **If you develop fever, tell the doctor immediately.**
- **Adhere to the use and dosage instructions and change the patch after 7 days, on the same day of the week and at the same time of the day.**
- **If your breathing becomes shallow and weak, remove the patch and seek medical help.**

Read the entire leaflet carefully before using the medicine.

This leaflet contains concise information about the medicine. Keep the leaflet in case you need to read it again. If you have further questions, refer to the doctor or the pharmacist.

This medicine has been prescribed for treatment of your condition. 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.

Medicines from the opioid group may cause addiction, especially with prolonged use, and have the potential for abuse and overdose. A reaction to an overdose can be manifested by slow breathing and even cause death.
Make sure you know the name of the medicine, the dosage you are taking, the frequency of administration, the duration of treatment, and the potential side effects and risks.
Additional information regarding the risk of dependence and addiction can be found at the link:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/opioids_en.pdf

Taking this medicine with medicines from the benzodiazepine group, with other medicines that depress the central nervous system (including drugs) or with alcohol, may cause a feeling of profound drowsiness, breathing difficulties (respiratory depression), coma and death.

1. What is the medicine intended for?

The medicine is intended for the relief of moderate to severe chronic pain that does not respond to non-opioid analgesics.

Therapeutic group: opioid analgesic.

This medicine has been prescribed for you only and should not be passed to anyone else. Opioids may cause addiction and you may experience withdrawal symptoms if you stop taking them suddenly. Make sure you receive an explanation from the doctor on the duration of treatment with the medicine, when to stop taking it and how to do so safely.

Butrans patches are not intended to relieve acute pain.

Butrans patches work through the skin. After application, the active ingredient (buprenorphine) passes through the skin into the blood. Each patch works for seven days.

2. Before using the medicine

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient (buprenorphine) or to any of the additional ingredients the medicine contains (see section 6), or if you have previously experienced an allergic skin reaction to patches containing buprenorphine.
- You suffer from a condition that affects or may affect your breathing (for example, severely impaired function of the respiratory system or severe damage to the respiratory center in the brain). The symptoms may include breathlessness, coughing or breathing more slowly or weakly than expected.
- You suffer from an addiction (dependence) to drugs or opioids, or are in the process of withdrawal from drugs or opioids. Do not use **Butrans** for treatment of symptoms associated with drug or opioid withdrawal.
- You are taking medicines for the treatment of depression from the monoamine oxidase inhibitor group (for example: tranylcypromine, phenelzine, isocarboxazid, moclobemide and linezolid), or if you have taken such a medicine within the past two weeks (see section "Drug interactions").
- You suffer from myasthenia gravis (muscle weakness).
- You have previously suffered from withdrawal symptoms (such as: agitation, anxiety, shaking, sweating) upon stopping drinking alcohol.

Special warnings regarding the use of the medicine:

Talk to your doctor, pharmacist or nurse before using **Butrans** patches:

Tolerance, dependence and addiction

This medicine contains buprenorphine, which is an opioid. Long-term use of opioids may lead to a decrease in the effectiveness of the medicine (you become used to it, which is known as tolerance). In addition, long-term use of **Butrans** may lead to dependence, abuse and addiction, which can result in a life-threatening overdose. The risk of these side effects may increase with a higher dose and a longer duration of use.

Dependence and addiction can make you feel that you are no longer in control of how much medicine you need to take or how often you need to take it. The risk of dependence and addiction varies from person to person. You may be at a greater risk of becoming dependent on or addicted to **Butrans** if:

- You or anyone in your family has ever been addicted to or developed a dependence on alcohol, prescription medicines or drugs ("addiction").
- You smoke.
- You suffer or have previously suffered from mood-related problems (depression, anxiety or personality disorder) or if you are treated or have been treated by a psychiatrist in the past for mental illnesses.

If you notice any of the following signs during treatment with **Butrans**, this could be a sign that you have developed a dependence or addiction:

- You need to take the medicine for longer than instructed by your doctor.
- You need to take more than the dose prescribed for you.
- You may feel that you need to continue taking the medicine, even when it doesn't help relieve your pain.
- You are using the medicine for reasons other than that for which it was prescribed for you, for example, "to stay calm" or "to help you sleep".
- You have made repeated, unsuccessful attempts to stop or control the use of the medicine.
- When you stop taking the medicine, you feel unwell, and your feeling improves when you take the medicine again ("withdrawal effects").

If you notice any of these signs, consult your doctor regarding the best treatment pathway for you, including when to stop treatment and how to stop it safely (see section 3, "If you stop using the medicine").

Before (and during) treatment with Butrans, tell the doctor if:

- You suffer from depression or from other conditions treated with antidepressants. Using these medicines together with **Butrans** may lead to serotonin syndrome, a condition which may be life-threatening (see section "Drug interactions").
- You suffer or have suffered in the past from fits of convulsions or seizures. You may experience these fits more frequently while using the medicine.
- You suffer from a brain injury or tumor, head injury, severe headache or nausea, when these may indicate an increased intracranial pressure. This is because **Butrans** may worsen the symptoms or mask the severity of the head injury.
- You suffer from a decrease in the level of consciousness or symptoms of shock, which can include: pale, cold and clammy skin, dizziness or light-headedness, fast and shallow breathing, or sweating.
- You suffer from dizziness or fainting spells.
- You have severe liver problems.
- You have recently had an operation.
- You have a high fever, as this may lead to the absorption of larger than normal amounts of the active ingredient into the blood. If you develop a fever, tell the doctor immediately.
- You suffer from severely impaired lung function. The symptoms may include breathlessness and coughing. See also section "Do not use the medicine if".
- You suffer from a condition in which your breathing stops for short time periods while you are sleeping, a condition known as sleep apnea.
- You suffer from constipation.

Additional warnings:

- Using this medicine regularly, especially for a long time period, may cause addiction. Make sure you receive an explanation from the doctor on the duration of treatment with the medicine, when to stop using it and how to do so safely.
- In rare cases, increasing the dosage of the medicine may make you more sensitive to pain. In this case, consult the doctor regarding the treatment.
- Addiction can cause withdrawal symptoms when you stop using the medicine. Withdrawal symptoms can include restlessness, sleeping difficulties, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, nausea, vomiting, diarrhea, loss of appetite, shaking, shivering or sweating. Before discontinuing the use of the medicine, consult the doctor who will instruct you how to decrease the dosage gradually. It is important that you do not stop using the medicine suddenly, as the risk of experiencing withdrawal symptoms will increase (see "If you stop using the medicine" in section 3).
- Opioids are intended to be used only by the patient they are prescribed for. Do not give the medicine to anyone else. Taking higher or more frequent doses of opioids increases the risk of addiction. Overuse and abuse can lead to an overdose and even to death.
- Sleep-related breathing disorders: the medicine may cause sleep-related breathing disorders, such as sleep apnea (breathing pauses during sleep) and sleep-related hypoxemia (low levels of oxygen in the blood). The symptoms may include: breathing pauses during sleep, night awakening due to shortness of breath, sleeping difficulties or excessive drowsiness during the day. If you or someone around you notices that you have these symptoms, refer to the doctor. The doctor may consider reducing the dosage.
- When using **Butrans** patches, you may experience mild to moderate skin reactions where the patch has been applied (contact dermatitis). These reactions include: redness, swelling, itching, rash, small blisters and pain or stinging/burning sensation at the application site. In certain cases, these reactions can be severe. In some cases, the reaction may only begin after several months of treatment.
  Using the patches according to the instructions in section 3 "How to use the medicine?" (see "Method of use") reduces the risk of experiencing these reactions.
  If you experience these symptoms, remove the patch immediately and refer to the doctor. Continued use of the patches after experiencing an allergic reaction may cause the appearance of blisters on the skin, open wounds, bleeding, ulceration, infections, changes to the skin color (hypo/hyper-pigmentation) and dry, thick, scaly, scar-like patches.
- The medicine is not intended to relieve acute pain. Due to the increased risk of dependence and of developing severe breathing problems, do not use **Butrans** patches if you have pain that lasts only for a short time or in case of post-operative pain. If you are about to have surgery or if you have just had surgery, please tell the doctor at the hospital if you are being treated with **Butrans** patches and discuss with him a plan for managing your pain.
- You should occasionally check (visually or by touch) the site where the patch is applied, to make sure that it is properly affixed, not loose and has not fallen off. If the patch is not properly affixed, attach it to the skin using an adhesive bandage (around the edges of the patch). Do not try to remove the patch and apply it elsewhere!

Children and adolescents:

This medicine is not intended for children and adolescents under the age of 18.

Tests and follow-up:

- It is recommended to schedule a follow-up appointment with the doctor a week or two after starting treatment, to make sure that the prescribed dosage is best for you and to check whether you suffer from any side effects of the medicine.
- In patients with liver diseases, the doctor may perform closer monitoring.
- During long-term treatment, you should undergo periodic evaluations in order to evaluate the ongoing need for the medicine.

Drug interactions

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or the pharmacist. Certain medicines may increase the side effects of Butrans and may sometimes cause very serious reactions.

In particular, you should inform the doctor or pharmacist if you are taking the following medicines (note that the following list mentions the active ingredients in the medicines. If you are not sure whether you are using any of these medicines, please consult the doctor or pharmacist):

Using **Butrans** concomitantly with other medicines that depress the central nervous system may cause slow breathing or difficulty breathing (respiratory depression), severe sleepiness, loss of consciousness and death. For this reason, the doctor will consider using **Butrans** together with these medicines only if there are no other treatment options available, and only at a low dosage and for short periods. These medicines include:

Other opioids for pain relief or cough suppression (such as: morphine, dextropropoxyphene, codeine, dextromethorphan or noscapine); antidepressants; medicines for treatment of allergy, motion sickness or nausea (antihistamines or anti-nausea); sleep-inducing medicines (such as benzodiazepines); medicines for treatment of anxiety; medicines for treatment of mental or psychiatric problems (such as phenothiazines); anesthetics (such as halothane); medicines for the treatment of high blood pressure (such as clonidine); medicines from the group of monoamine oxidase inhibitors (MAOIs) for the treatment of depression, such as: tranylcypromine, phenelzine, isocarboxazid, moclobemide, linezolid. Do not use **Butrans** if you are taking, or have taken in the last two weeks, medicines from the MAOIs group; gabapentin or pregabalin for treatment of epilepsy or pain due to nerve problems (neuropathic pain); muscle relaxants; medicines for the treatment of Parkinson's disease.

If you or those around you (friends, family, caregivers) notice that you are having difficulty breathing or have become very sleepy or have lost consciousness, it is necessary to refer to a doctor immediately.

Antidepressants, such as: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepin or trimipramine or other serotonergic medicines: these medicines may interact with **Butrans** patches – serotonin syndrome which may be life-threatening, and you may experience symptoms such as: involuntary and rhythmic muscle contractions, including the muscles that control eye movement, agitation, hallucinations, coma, excessive sweating, tremor, increased reflexes, increased muscle tension, gastrointestinal symptoms, body temperature above 38°C. Refer to the doctor if you feel these symptoms.

Medicines that may reduce the effect of **Butrans**, such as: phenobarbital, phenytoin (medicines usually used for treatment of epileptic fits, seizures and convulsions), carbamazepine (a medicine for treatment of epileptic fits, seizures, convulsions and certain types of pain), rifampicin (for the treatment of tuberculosis).

Use of the medicine and alcohol consumption:

Do not drink alcohol during the period of treatment with this medicine. Alcohol may worsen some of the side effects of the medicine and may make you feel unwell. In addition, drinking alcohol while using **Butrans** patches may affect your reaction time.

Pregnancy and breastfeeding:

- **Pregnancy:** do not use **Butrans** patches if you are pregnant, think you are pregnant or are planning a pregnancy, unless you have discussed this with the doctor who prescribed the medicine, and the benefits of treatment outweigh the potential harm that may be caused to the baby. If the medicine is used during pregnancy, it may cause respiratory depression in the newborn and the baby may also develop dependence on the medicine and experience withdrawal symptoms after the birth, which may require treatment. The symptoms may include: agitation, hyperactivity, abnormal sleep patterns, high pitched crying, shaking, vomiting, diarrhea, not putting on weight.
- **Labor:** use during labor may cause respiratory depression in the newborn, which will require appropriate treatment after the birth.
- **Breastfeeding:** do not use the medicine during the breastfeeding period, as the active ingredient (buprenorphine) passes into breastmilk and may affect the baby (may cause respiratory depression in the baby).
- In addition, **Butrans** patches should not be used in women who may become pregnant and who are not using effective contraception.

Consult with the doctor or the pharmacist before using this medicine.

Driving and use of machinery:

- Using this medicine may impair alertness and the ability to react to such an extent that you will not be able to react properly or quickly enough to unexpected or sudden occurrences. This applies particularly: at the beginning of treatment, when the dosage is increased, in combination with alcohol, in combination with medicines to treat anxiety or help you sleep.
- Do not drive while using the medicine until you know how it affects you.
- If you experience effects such as: dizziness, drowsiness, blurred vision, do not drive or operate machinery while using **Butrans** patches and for 24 hours after removing the patch.
- In any case, caution should be exercised when driving a vehicle, operating dangerous machinery and during any activity that requires alertness (including for about 24 hours after removing the patch).

Talk to your doctor or a pharmacist if you are not sure whether it is safe for you to drive while using this medicine.

3. How to use the medicine?

Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and manner of treatment with the medicine.

Before starting the treatment and regularly during treatment, your doctor should discuss with you what to expect while using **Butrans**, when and for how long you need to use the medicine, when to refer to the doctor and when to discontinue treatment (see also "If you stop using the medicine").

Butrans patches are available in several strengths. The dosage and treatment regimen will be determined by the doctor only.

When patients first start using the medicine, they often experience some nausea and vomiting (see section 4 in this leaflet). Generally, these effects pass after the first week of treatment. It is recommended to schedule a follow-up appointment with your doctor a week or two after starting treatment with **Butrans** patches, to make sure that you are taking the appropriate dosage and to treat any potential side effects.

Make sure that the doctor who prescribed you the medicine discusses with you the duration of treatment with the medicine, the plan for discontinuing treatment and how to discontinue taking the medicine gradually.

The generally accepted dosage is:

One patch is usually intended for treatment of seven consecutive days, and should be replaced with a new patch every seven days (once a week on the same day of the week), preferably at the same time each time. If necessary, the doctor may change the dosage after 3 to 7 days, until the proper level of pain control is achieved.

Leave the patch on the skin for 3 full days before increasing the dosage, as the maximum effect of the dose is achieved after 3 days.

In any case, do not use more than two patches at the same time, and up to a maximum dose of 40 micrograms per hour.

Do not exceed the recommended dose.

This medicine should be used at set intervals as determined by the attending doctor.

During the treatment, the doctor may instruct you to use a higher or lower dosage, or a combination of up to two patches. Do not cut or divide the patch.

If your doctor has advised you to take other pain relievers in addition to the **Butrans** patch, strictly follow the doctor's instructions, otherwise, you will not fully benefit from the treatment with **Butrans**.

Patients with a kidney disease/dialysis patients: in patients with a kidney disease, no special dose adjustment is required.

Patients with liver disease: in patients with a liver disease, the effects and duration of action of the **Butrans** patch may vary, and therefore, your doctor may monitor your condition more closely.

Note:

This medicine is intended for external use only.

Method of use:

a. Before applying the patch

- Choosing the application site: choose a dry, clean area that is not irritated or red and not injured, without large scars and without hair (or with little hair), on your upper body (chest or back) or on the outer part of your upper arms (see Figure 1). If you cannot apply the patch yourself, ask for assistance.

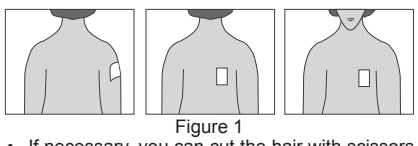
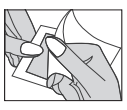
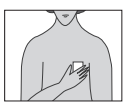


Figure 1

- If necessary, you can cut the hair with scissors (do not shave), at the site intended for application. Avoid applying on an area in which the skin may fold.
- If the area intended for application needs to be cleaned, wash it with cold or lukewarm water only (not hot). Do not use soap, alcohol, oils, emulsions or other detergents (cleaning materials).
  After a hot shower or bath or on hot and humid days – it is important to ensure that the skin is completely dry and has cooled down to normal temperature, before applying the patch. Do not apply any emulsion, cream or ointment on the site intended for applying the patch. This may prevent the patch from sticking properly.

b. Applying the patch





Step 1: each patch comes in a sealed sachet. Open the sachet just before use. Be careful not to damage the patch while opening the sachet. Take the patch out of the sachet. Do not use the patch if the sachet was not hermetically sealed. Apply the patch immediately after taking it out of the sachet.

Step 2: the sticky side of the patch is covered with a silvery protective foil. Carefully peel off half the foil. Try not to touch the sticky part of the patch.

Step 3: apply the patch to the skin on the chosen area and remove the remaining part of the foil.

Step 4: press on the patch using the palm of your hand and count slowly to 30. Make sure that the entire patch surface is in contact with your skin, especially at the edges.

Write down the date and time of applying the patch.

c. While the patch is affixed to the skin

- Generally, the patch should be left on the skin for seven consecutive days (a week).
- If the patch has been properly applied, the chance of it falling off is low. If the edges of the patch start to peel off from the skin, attach them using an adhesive bandage or adhesive tape suitable for skin (around the patch).
- Wait at least one hour from the moment the patch is applied, before performing physical activity that causes sweating or before wetting the site of application.
- You can bathe or swim while the patch is attached to the skin.
- Do not expose the application site to an external heat source (such as: heating pad, hot water bottle, electric sheet or blanket, heat lamps, sauna, hot baths/showers, jacuzzi, heated water beds, etc.), as this may lead to the absorption of larger amounts than normal of the active ingredient into the blood. External heat may also impair the adhesiveness. If you have high fever, this may change the effect of **Butrans** patches (see "Special warnings regarding the use of the medicine" in section 2).
- In the unlikely event that the patch falls off before you need to change it, do not use it again. Immediately apply a new patch (see "Changing the patch" below).

d. Changing the patch

- Remove the used patch and fold it in half with the sticky side inwards.
- Open a sachet containing a new patch and take out the patch. Put the used patch inside the empty sachet. Discard the used patch in a hidden and safe place.
- Even used patches contain a certain amount of active ingredient, which may harm children or animals. Therefore, make sure the used patches are kept out of their reach and sight.
- Apply the new patch on a different suitable site on your body (as described above). Do not apply the patch on the same site for the next 3 to 4 weeks.
- Remember to change the patch at the same time of day. It is important to write down the time of application.

e. Duration of treatment

- The doctor will instruct you how long you will be treated with **Butrans** patches. Do not stop the treatment without consulting the doctor, because your pain may return and you may feel unwell again (see the section "If you stop using the medicine" below).
- If you feel that the effect of the medicine is too weak or too strong, consult the doctor.
- Do not keep the remaining patches at home after the end of treatment with **Butrans**. If any unneeded patches remain, consult the pharmacist.

If you accidentally use a higher dosage:

Immediately upon discovering that you have used more patches than the doctor instructed you to, or if the patch has accidentally attached to a child or to anyone other than the patient, remove all patches, **refer immediately** to a doctor or to a hospital emergency room, and bring the medicine's package and its content with you, along with this leaflet. People who have taken an overdose may feel very sleepy, and suffer from nausea and vomiting. In addition, breathing difficulties and loss of consciousness may occur. Symptoms of an overdose require urgent medical assistance.

It is advisable to ask those around you to also be familiar with these symptoms and notice if you develop them.

If you forget to apply a patch or if you forget to change it:

Apply a patch as soon as you remember, and write down the new changing time (date and time). If you are very late changing your patch, your pain may return. In this case, consult with the doctor.

Never attach additional patches, beyond what the doctor has prescribed, to compensate for the forgotten application.

Adhere to the treatment as recommended by the doctor. Even if there is an improvement in your state of health, do not stop treatment with the medicine without consulting the doctor.

If you stop using the medicine:

- Do not stop using the medicine suddenly. If you want to stop using the medicine, consult the doctor first, who will guide you on how to do so. The doctor will usually advise you to reduce the dosage gradually to minimize unpleasant withdrawal symptoms, such as: restlessness, sleeping difficulties, irritability, agitation, anxiety, feeling your heartbeat (palpitations), increased blood pressure, nausea, vomiting, diarrhea, increased heart and/or breathing rate, loss of appetite, shaking, shivering, sweating, excessive secretions (tears, runny nose), yawning, muscle aches, dilated pupils, abdominal cramps, weakness, excessive movements (hyperkinesia).
- If you stop using **Butrans** patches too soon or interrupt the treatment continuity, your pain may return.
- The pain relieving effect of the **Butrans** patch is maintained for a while after removing the patch. Do not start using another opioid analgesic medicine (strong pain reliever) for 24 hours after removing the patch.

Do not use or take medicines in the dark! Check the label and the dose every time you use the medicine. Wear glasses if you need them.

If you have further questions regarding the use of the medicine, consult the doctor or the pharmacist.

4. Side effects

As with any medicine, using **Butrans** patches may cause side effects in some users. Do not be alarmed when reading the list of side effects, you may not experience any of them.

Side effects that require special attention:

- **Allergic reaction:** the medicine can cause allergic reactions, although a serious allergic reaction is rare. **Remove the patch and seek immediate medical attention if the following symptoms appear,** which may indicate a serious allergic reaction: sudden wheeziness, breathing difficulties, swelling of the eyelids, face or lips, rash or itching, particularly those that appear on the whole body.
- **Skin allergic reactions:** you may experience skin allergic reactions at the site of application. The symptoms may include rash, redness, itching, blisters, pain or stinging/burning sensation, inflammation or swelling of the skin. In certain cases, these reactions may be severe. If you experience these symptoms, **remove the patch and refer to the doctor.**
- **Respiratory depression:** the most serious side effect is a condition in which you breathe more slowly or weakly than usual (respiratory depression), which may lead to severe sleepiness and loss of consciousness. This side effect may occur in up to 1 out of 1,000 people and is more likely to occur when taken concomitantly with certain other medicines (see "Drug interactions" in section 2). **Remove the patch and refer to the doctor immediately if this side effect occurs.** It is recommended to ask those around you (friends, family, caregivers) to notice if you develop these signs and symptoms.
- **Withdrawal symptoms:** when you stop taking the medicine, you may experience withdrawal symptoms. See "If you stop using the medicine" in section 3.
- **Addiction: how to identify a state of addiction?** If you notice any of the following signs while using **Butrans** patches, this may be a sign of addiction: you feel a need to use the patches for a longer time period than the doctor recommended and/or take a higher dose than the doctor recommended; you are using the medicine for reasons other than those for which it was prescribed for you; when you stop using the medicine you feel unwell, and you feel better when you use it again. If you feel these symptoms, refer to the doctor.

Additional side effects:

Very common side effects (occur in more than one user out of ten):

- Headache, dizziness, drowsiness/sleepiness;
- Constipation, nausea, vomiting;
- Itchy skin, erythema;
- Skin reactions at the application site: rash, redness, itching, blisters, pain or stinging/burning sensation, inflammation or swelling of the skin.

Common side effects (occur in 1-10 users out of 100):

- Loss of appetite;
- Confusion, depression, anxiety, sleeping difficulties, nervousness, shaking (tremors);
- Shortness of breath;
- Abdominal pain or discomfort, diarrhea, indigestion, dry mouth;
- Sweating, rash, skin lesions;
- Tiredness, a feeling of unusual weakness, muscle weakness, swelling or edema in the hands, ankles or feet.

Uncommon side effects (occur in 1-10 users out of 1,000):

- Allergic reactions (hypersensitivity) including swelling of the face, lips or tongue, rash or itching;
- Loss of control of your mood, changes to your sleeping habits, restlessness, agitation, feeling of extreme happiness (euphoria), hallucinations, decreased sexual drive, nightmares, aggression;
- Severe sleepiness, changes in taste, difficulty in speaking, reduced sensitivity to pain or touch, numbness or tingling;
- Loss of memory, migraine, fainting, problems with concentration or coordination;
- Dry eyes, blurred vision;
- Ringing or buzzing in the ears, vertigo (feeling of dizziness or spinning);
- High or low blood pressure, chest pain, fast or irregular heartbeat, flushing of the skin;
- Cough, hiccups, wheezing;
- Wind;
- Weight loss;
- Dry skin, itchy raised skin rash (urticaria);
- Muscle cramps, muscle aches;
- Loss of bladder control (incontinence), difficulty starting to urinate, inability to fully empty the bladder, urinary retention;
- Extreme fatigue, fever, chills (sudden feeling of cold with a high temperature and sweating), fluid retention (edema);
- Increased accidental injuries (for example, falls);
- Withdrawal symptoms, such as: agitation, anxiety, sweating or shaking, when you stop using **Butrans** patches (see "If you stop using the medicine" in section 3);
- Changes in liver function (liver enzyme elevation in blood tests).

Rare side effects (occur in 1-10 users out of 10,000):

- Severe allergic reaction (anaphylactic shock), whose symptoms include: breathing difficulties, wheezing, severe swelling of the face, lips or tongue, rash or itching and loss of consciousness. See above "Side effects that require special attention";
- Angina pectoris (chest pain associated with heart disease);
- Severe mental disorder causing loss of touch with reality (psychotic disorder);
- Balance impairments;
- Changes in vision, swelling or puffiness of the eyelids or face, reduction in the size of the eye pupils;
- Breathing difficulties, worsening of asthma, very fast breathing (hyperventilation);
- Dilation of blood vessels, a feeling of faintness, particularly when standing up;
- Difficulty swallowing, intestinal obstruction;
- Swelling and irritation inside the nose (nose inflammation);
- Sexual function impairment, such as erectile dysfunction;
- A flu-like illness;
- Dehydration.

Very rare side effects (occur in less than one user out of 10,000):

- Mood swings;
- Involuntary muscle twitching;
- Ear pain;
- Blisters, pustules (inflamed pus-filled pimples).

Side effects with unknown frequency (effects whose frequency has not yet been determined):

- Seizures or convulsions;
- Inflammation of the bowel wall, whose symptoms can include: fever, vomiting, abdominal pain or discomfort;
- Colicky abdominal discomfort and pain which can be due to biliary colic;
- Feeling detached from oneself;
- Increased sensitivity to pain;
- Development of a condition in which your breathing stops for a short time during sleep, known as sleep apnea;
- A need for more patches to achieve the same level of pain relief (tolerance to the medicine);
- Dependence and addiction (see above "Addiction: how to identify a state of addiction?");
- Contact dermatitis (a skin rash with inflammation which can include a stinging/burning sensation), skin discoloration.

Prolonged use of **Butrans** patches during pregnancy may cause life-threatening withdrawal symptoms in the newborn. Symptoms to look out for in the baby: agitation, hyperactivity, abnormal sleep patterns, high pitched crying, shaking, vomiting, diarrhea, not putting on weight.

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 with the doctor.

Side effects may be reported to the Ministry of Health by clicking on the link "Report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which leads to the online form for reporting side effects, or by clicking on the link:
https://sideeffects.health.gov.il

5. How to store the medicine?

Avoid poisoning! This medicine particularly, as well as any other medicine, must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning.

Do not induce vomiting without an explicit instruction from the doctor.

- Do not use the medicine after the expiry date (exp. date) stated on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** store below 25°C. Make sure the patches are kept in the original aluminum sachet.
- Store the medicine in a closed, safe place, where other people cannot access it. The medicine can cause severe harm and even death to people who accidentally or intentionally use it, when the medicine has not been prescribed for them.
- Do not use this medicine if the patch or its package is damaged.
- A used patch should be folded in half with the sticky side inwards, and disposed of in a safe place away from the reach and sight of children (see subsection D – "Changing the patch" under "Method of use" in section 3). Do not discard medicines via wastewater or household waste. Consult the pharmacist on how to dispose of the patches. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient, the patches also contain:

DuroTak 387-2051 (polyacrylate adhesive without cross linker), DuroTak 387-2054 (polyacrylate adhesive with cross linker), oleyl oleate, levulinic acid, povidone K90, polyethylene terephthalate.

What does the medicine look like and what does the package contain?

Each package contains 2 beige transdermal patches. Each patch is packed in a separate aluminum sachet.

Butrans 5: square patches with an area of 6.25 cm². The back of the patch is imprinted with 'BuTrans 5 µg/h' in blue ink.

Butrans 10: rectangular patches with an area of 12.5 cm². The back of the patch is imprinted with 'BuTrans 10 µg/h' in blue ink.

Butrans 15: rectangular patches with an area of 18.75 cm². The back of the patch is imprinted with 'BuTrans 15 µg/h' in blue ink.

Butrans 20: square patches with an area of 25 cm². The back of the patch is imprinted with 'BuTrans 20 µg/h' in blue ink.

Registration holder: Rafa Laboratories Ltd., P.O. Box 405, Jerusalem 9100301, Israel.

Manufacturer: LTS Lohmann Therapie Systeme AG, Germany.

Medicine registration numbers in the national medicines registry of the Ministry of Health:

Butrans 5: 135-70-31151
Butrans 10: 135-71-31152
Butrans 15: 157-99-34931
Butrans 20: 135-72-31153

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