DIPHERELINE® S.R. 11.25 mg

powder and solvent for suspension for injection (I.M.), 3-month prolonged release form

Triptorelin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

1. What DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3- month prolonged release form is and what it is used for?
2. What you need to know before you use DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form?
3. How to use DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form?
4. what are the possible side effects?
5. How to store DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form?
6. Contents of the pack and other information

1. WHAT DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form IS AND WHAT IT IS USED FOR?

Pharmacotherapeutic group: gonadotropin releasing hormone analogues - ATC code: L02AE04.

This medicine is an analogue of a natural hormone.

It is used:

In adult men:

- for the treatment of locally advanced or metastatic, hormone-dependent prostate cancer.
- for the treatment of high risk localised or locally advanced hormone-dependent prostate cancer in combination with radiation therapy

In women:

- for the treatment of endometriosis.

In children:

- for the treatment of puberty that occurs at a very young age, i.e. before 8 years in girls and 10 years in boys (central precocious puberty).

2. WHAT YOU NEED TO KNOW BEFORE YOU USE DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form?

Do not use DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form

- If you are allergic (hypersensitive) to triptorelin, gonadotropin releasing hormone (GnRH), other GnRH analogues or any of the excipients of this medicine, listed in section 6.
- If you are pregnant or breast-feeding.

Warnings and precautions

Talk to your doctor or pharmacist before taking DIPHERELINE S.R. 11,25 mg.

- There have been reports of depression in patients taking DIPHERELINE S.R. 11,25 mg which may be severe. If you are taking DIPHERELINE S.R. 11,25 mg and develop depressed mood, inform your doctor. Your doctor may want to monitor your depression during treatment.
- If you have an enlargement (benign tumor) of the pituitary gland that you were unaware of, this may be discovered during treatment with DIPHERELINE S.R. 11.25 mg, which can lead to bleeding from the tumor (pituitary apoplexy). Symptoms include sudden headache, vomiting, problems with eye sight and paralysis of the eyes.
- If you are using medicines for preventing your blood clotting (anticoagulant), since you may experience bruising at the site of injection.

In men

- At the beginning of treatment there will be an increased amount of testosterone in your body. This may cause the symptoms of the cancer to get worse. Contact your doctor if this happens. The doctor may give you some medicine (an anti-androgen) to prevent your symptoms from getting worse.
- If you suffer from urinary obstruction or spinal cord (nerves in your backbone) compression due to your prostate cancer spreading, your doctor will supervise you closely for the first few weeks of treatment. If you experience difficulty passing urine, bone pain, weakness of lower limbs or pins and needles sensation, contact your doctor immediately, who will assess and treat you appropriately.
- After surgical castration triptorelin does not induce any further decrease in serum testosterone levels.
- Diagnostic tests of pituitary gonadal function conducted during treatment or after discontinuation of therapy with DIPHERELINE S.R. 11.25 mg may be misleading.
- In adults, triptorelin may cause thinning of the bones (osteoporosis) with an increased risk of bone fractures. You should therefore tell your doctor if you have any of the below risk factors as he/she might give you bisphosphonate (drugs used to treat weak bones) to treat bone loss. Risk factors may include:
  - If you or any of your close family have thinning of the bones.
  - If you drink excessive amounts of alcohol, and/or smoke heavily and/or have a poor diet.
  - If you take medicines over a long period of time that may cause thinning of the bones, for example medicines for epilepsy or steroids (such as hydrocortisone or prednisolone).
- If you have any heart or blood vessel conditions, including heart rhythm problems (arrhythmia), or are being treated with medicines for these conditions. The risk of heart rhythm problems may be increased when using DIPHERELINE S.R. 11,25 mg.
- Testosterone decreasing agents may cause changes in ECG associated with heart rhythm abnormalities (QT prolongation).
- If you have diabetes or if you suffer from heart problems, inform your doctor.
- Biological controls may be required during treatment to verify efficacy.
- The testosterone deprivation can induce anemia (decrease of the number of red blood cells).

In women

- In adults, triptorelin may cause thinning of the bones (osteoporosis) with an increased risk of bone fractures. You should therefore tell your doctor if you have any of the below risk factors as he/she might give you bisphosphonate (drugs used to treat weak bones) to treat bone loss. Risk factors may include:
  - If you or any of your close family have thinning of the bones.
  - If you drink excessive amounts of alcohol, and/or smoke heavily and/or have a poor diet.
  - If you take medicines over a long period of time that may cause thinning of the bones, for example medicines for epilepsy or steroids (such as hydrocortisone or prednisolone).
- Due to lack of clinical experience in women under 18 years of age, Triptorelin is not recommended in adolescent and young women as it might cause thinning of bone.
- You may have some vaginal bleeding in the first month of treatment. After that your periods normally stop. Tell your doctor if you have bleeding after the first month of treatment.
- Your periods should start approximately 5 months after the last injection.
- You must use some form of contraception other than the 'pill' during all the treatment and till the menses are back.
- Patients receiving this treatment should be kept under close medical supervision with strict and regular biological, clinical and echographic controls.

In children

- Girls who have an early puberty may have some vaginal bleeding in the first month of treatment.
- If you have a progressive brain tumor, please inform your doctor. This may affect the way your doctor decides to treat you.
- When treatment is stopped signs of puberty will occur.
- In girls, menstrual bleeding will start on average one year after stopping treatment.
- Early puberty caused by other diseases should be ruled out by your doctor.
- The amount of minerals in the bones decreases during treatment but this returns to normal after treatment is stopped.
- A pathology of the hip may occur after stopping treatment (slipped capital femoral epiphysis of the hip). It results in stiffness of the hip, a limp and / or severe pain in the groin radiating to the thigh. If this occurs, you should consult your doctor.
- If your child suffers from a bad or recurrent headache, problems with eyesight and ringing or buzzing in the ears, contact a doctor immediately (see section 4).

If you or your children are concerned by any sign listed above, talk to your doctor.

Other medicines and DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

In men:

DIPHERELINE S.R. 11,25 mg might interfere with some medicines used to treat heart rhythm problems (e.g. quinidine, procainamide, amiodarone and sotalol) or might increase the risk of heart rhythm problems when used with some other drugs e.g. methadone (used for pain relief and part of drug addiction detoxification), moxifloxacin (an antibiotic), antipsychotics (used for serious mental illnesses).

DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form with food and drink

Not applicable.

Pregnancy and breast-feeding

This medicine should not be used during pregnancy or breast-feeding.

Do not use DIPHERELINE S.R. 11,25 mg if you are trying to get pregnant. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

You may feel dizzy, tired or have problems with your sight such as blurred vision. These are possible side effects of treatment or from the underlying disease. If you experience any of these side effects, you should not drive or use machines.

DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form contains sodium.

This medicine contains sodium, but less than 1 mmol (23 mg) sodium per vial, i.e. essentially « sodium free ».

3. HOW TO USE DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form?

Posology

One injection every 3 months.

If you have the impression that the effect of DIPHERELINE S.R. 11,25 mg is too strong or too weak, talk to your doctor or pharmacist.

Method and route of administration

Intramuscular route.

The powder should be reconstituted with the solution provided immediately before injection. The suspension obtained should not be mixed with other medicinal products.

N.B.: The injection should be prepared in strict compliance with the instructions given below. Any incomplete injections resulting in the loss of suspension volumes greater than the volume generally remaining in the injection syringe must be reported.

Duration of treatment

The treatment in women should not be given for more than 6 months.

If you take more DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form, than you should

Ask immediately your doctor or pharmacist.

If you forget to take DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form

Ask your doctor.

Do not take a double dose to make up for forgotten individual doses.

Effects when treatment with DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form, is stopped

In women, recovery of ovarian activity (ovulation possibility, menses).

If you have any further questions on the use of this medicine, ask your doctor, or pharmacist.

4. WHAT ARE THE POSSIBLE SIDE EFFECTS?

Like all medicines, this medicine can cause side effects, although not everybody gets them.

In rare cases you may experience a severe allergic reaction (angioedema, anaphylactic reaction). Tell your doctor immediately if you develop symptoms such as swallowing or breathing problems, dizziness, swelling of your lips, face, throat or tongue, a rash.

In men

Most side effects are expected, due to the change in testosterone in the body. These effects include hot flushes, impotence and decreased libido.

Very common side effects (affecting more than 1 patient in 10)

- Libido decrease.
- Pins and needles sensation in the legs.
- Hot flushes.
- Excessive sweating.
- Back pain.
- Impotence.
- Weakness.

Common side effects (affecting 1 to 10 patients in 100)

- Decrease of red blood cells (anemia).
- Allergic reaction.
- Depression, mood changes, loss of libido.
- Dizziness, headache.
- High blood pressure.
- Dry mouth, nausea.
- Muscle and bone pain, pain in the arms and legs.
- Lower abdominal pain.
- Reaction at the injection site (redness, inflammation and pain), oedema (build-up of fluid in the body tissues).
- Increase in weight.

Uncommon side effects (affecting 1 to 10 patients in 1000)

- Increase in blood platelets.
- Loss of appetite, diabetes, gout (severe pain and swelling in the joints usually in the big toe), excessive lipids in the blood, increase of appetite.
- Inability to sleep, feeling of irritability.
- Tingling or numbness.
- Vision disorders.
- Ringing in the ears, vertigo.
- Feeling your heartbeat.
- Difficulty in breathing, nose bleeding.
- Pain in abdomen, constipation, diarrhoea, vomiting.
- Acne, hair loss, redness of skin, itching, rash, urticaria.
- Joint pain, bone pain, muscle cramp, muscle weakness, muscle pain.
- To wake up to pass urine, problems passing urine.
- Breast swelling, breast pain, reduction in testicular size, pain in testicles.
- Drowsiness, swelling of ankles, feet and fingers, pain, shaking, sleepiness.
- Some blood tests affected (including raised liver function tests), blood pressure increased, weight loss.

Rare side effects (affecting 1 to 10 patients in 10,000)

- Inflammation of the nose/throat.
- Feeling confused, decreased activity, having a feeling of relation or well-being.
- Memory loss.
- Abnormal sensation in the eye, abnormal vision.
- Low blood pressure.
- Shortness of breath when lying flat.
- Sensation of fullness in the abdomen, abnormal sense of taste, flatulence.
- Blisters, red and purple discoloration on the skin.
- Stiff joints, joint swelling, musculoskeletal stiffness, osteoarthritis.
- Chest pain, difficulty in standing, flu-like symptoms, fever.

Frequency not known (cannot be estimated from the available data)

- Serious allergic reaction which causes swelling of the face, tongue and neck, dizziness or difficulty of breathing (Quincke oedema, anaphylactic shock).
- Anxiety.
- If an existing pituitary tumor, an increased risk of bleeding to the area (pituitary apoplexy).
- Electrocardiogram changes (QT interval prolongation).
- Urinary incontinence.
- General discomfort.

Like with other analogues of GnRH, an increase of white blood cells can be observed with DIPHERELINE S.R. 11,25 mg.

Patients receiving long-term treatment by GnRH analogue in combination with radiation may have more side effects especially gastrointestinal, related to radiotherapy.

In women

Many of the side effects are expected due to the change in the level of estrogens in your body.

Very common side effects (concern more than 1 patient in 10)

•Difficulty in sleeping, mood swings, decreased libido •Headache •Hot flushes •Acne, excessive sweating, oily skin •Breast disorder •Pain during or after sexual intercourse, genital bleeding, ovarian hyperstimulation syndrome (with increase of the size of ovaries and water retention), ovaries size increase, pelvic pain, dryness of the vagina • Weakness

Common side effects (concern 1 to 10 patients in 100)

•Allergic reaction •Depression (long term treatment), nervousness •Dizziness •Nausea, abdominal pain or discomfort •Painful joints, muscle cramps, pain in the arms and legs •Breast pain •Reaction at the injection site (including pain, swelling, redness, inflammation) • Swelling of ankles, feet and fingers •Weight gain

Uncommon side effects (concern 1 to 10 patients in 1000)

•Decreased appetite •Water retention •Mood changes, anxiety, depression (short term treatment), disorientation •Abnormal taste, loss of sensations, temporary loss of consciousness, memory loss, lack of concentration, tingling or numbness, involuntary muscle movement. •Dry eye, blurred vision •Vertigo •Feeling your heartbeat •Difficulty breathing, nosebleed •Sensation of fullness in the abdomen, diarrhea, dry mouth, flatulence, mouth ulcer, vomiting • Hair loss, dry skin, excessive bodily hair, brittle nails, itching, skin rash •Back pain, muscle pain •Bleeding after sex, prolapse, painful period, irregular period, heavy period, small cysts (swelling) on the ovaries which can cause pain, discharge from the vagina •Weight decrease

Side effects reported during post-marketing surveillance (frequency cannot be estimated from the available data)

•Serious allergic reaction which causes swelling of the face, tongue and neck, dizziness or difficulty of breathing (Quincke oedema, anaphylactic shock) •Confusion •Visual disturbance •If an existing pituitary tumor, an increased risk of bleeding to the area •Increased blood pressure •Urticaria •Muscle weakness •Absence of menstrual periods •Fever, general discomfort •Some blood test affected (including raised liver function tests)

In endometriosis treatment, the disorders for which the treatment has been justified (pelvic pain, dysmenorrhea) may be exacerbated at the beginning of the treatment, but should disappear in one to two weeks. This may occur even if the treatment is producing a favorable effect. You should nevertheless immediately notify your doctor of this phenomenon.

In children

Very common side effects (affect 1 to 10 patients of 10)

•Vaginal bleeding may occur in girls in the first month of treatment

Common side effects (affect 1 to 10 patients of 100)

•Allergic reactions •Headache •Hot flushes •Pain in abdomen •Acne •Pain bruising, redness and swelling at injection site •Weight gain

Uncommon side effects (affect 1 to 10 patients of 1000)

•Overweight •Changes in mood •Blurred vision •Nosebleeds •Vomiting, constipation, nausea •Itching, rash or hives in the skin •Neck pain •Pain in breast •General discomfort

During the post-marketing surveillance, the following side effects have also been reported (their frequency cannot be estimated from the available data)

•Serious allergic reaction which can lead to a swelling of the face, the tongue and the neck, dizziness or breathing difficulties (Quincke oedema, anaphylactic shock) •Mood disorders, depression, nervousness •Abnormal vision •High blood pressure •Muscle pain •Some blood tests affected include hormone levels •Idiopathic intracranial hypertension (increased intracranial pressure around the brain characterized by headache, double vision and other visual symptoms, and ringing or buzzing in the ears)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system.

By reporting side effects, you can help provide more information on the safety of this medicine.

5. HOW TO STORE DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form?

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the box and on the labels after EXP. The expiry date refers to the last day of that month.

The reconstituted suspension must be used immediately.

Do not store DIPHERELINE S.R. 11,25 mg above 30 °C.

Do not use DIPHERELINE S.R. 11,25 mg if you notice any visible signs of deterioration on packaging or blisters. Inform your pharmacist.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6.CONTENT OF THE PACK AND OTHER INFORMATION

What DIPHERELINE S.R. 11,25 mg, powder and solvent for suspension for injection (I.M.), 3-month prolonged release form contains?

- The active substance is :

Triptorelin...11.25 mg*

(as triptorelin pamoate)

Per dosage unit

* Taking into account the characteristics of the pharmaceutical form, each vial contains a quantity of triptorelin pamoate corresponding to 15 mg of triptorelin.

- The other ingredients are :

Powder: Poly (d,l-lactide-co-glycolide), mannitol, carmellose sodium, polysorbate 80.

Solvent: Mannitol, water for injections.

What DIPHERELINE S.R. 11,25 mg looks like and contents of the pack?

This medicinal product is a powder and solvent for prolonged-release suspension for injection (I.M.). Pack of 1 vial of powder + 1 ampoule of solvent + 1 syringe + 2 needles.

Manufacturer: **Darlan Darou** Pharmaceutical Co.-IRAN

Under license of **IPSEN PHARMA**-FRANCE

دیفرلین® آهسته رهش ۱۱/۲۵ میلی‌گرم

پودر و حلال برای تهیه سوسپانسیون تزریقی

فرم آهسته رهش ۳ ماهه

تریپتورلین

The following information is intended for healthcare professionals only (see section 3):

INSTRUCTIONS FOR USE

Read carefully the leaflet before injection.

1 – PREPARATION OF THE PATIENT BEFORE RECONSTITUTION

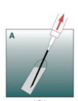
Prepare the patient by disinfecting his gluteus at the injection site. This operation needs to be performed first because once reconstituted, the drug should be injected immediately.

2 – PREPARATION OF THE INJECTION

The presence of bubbles on top of the lyophilisate is a normal appearance of the product.

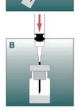
- Take out the ampoule containing the solvent. Tap any solution within the tip of the ampoule back to the main body of the ampoule.
- Take out the vial containing the powder; Tap any powder which has accumulated at the top of the vial back to the bottom of the vial.
- Remove the plastic tab on top of the vial.
- Screw a needle onto the syringe. Do not remove the needle protection yet.
- Break open the ampoule with dot face up.
- Remove the needle protection from the needle. Insert the needle in the ampoule and draw up all the solvent into the syringe.

A



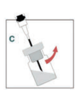
- Insert the needle through the rubber stopper vertically into the vial. Inject the solvent slowly, so that, if possible, it washes down the entire upper part of the vial.

B



- Pull up the needle above the liquid level and reconstitute the suspension by swinging the vial gently, which means shaking horizontally.
- Make sure that the agitation is long enough to obtain a homogeneous and milky suspension.
- **Check there is no unsuspended powder in the vial** (if any powder clumps are present, continue swirling until they disappear)

C



- When the suspension is homogeneous, pull down the needle and draw up all of the suspension (without inverting the vial). A small amount will remain in the vial and should be discarded. An overfill is included to allow for this loss.

D

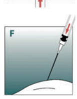
- Grasp the coloured hub to connect needle. Remove the needle used for the reconstitution from the syringe. Attach the other needle to the syringe tip (screw on tightly).
- Remove the needle protection from the needle.

E

3 – INTRAMUSCULAR INJECTION

Prime the needle to remove air from the syringe immediately before administrating the injection. To avoid precipitation, inject immediately into the gluteal muscle previously disinfected.

F



4 – AFTER USE

- Dispose the needles in designated sharp container.

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