

In the name of God

Ziferon® 250 microgram/ml

Interferon beta-1b

Lyophilized powder and solvent for solution for injection

Read all Ziferon 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, pharmacist or Medical Support Team of Zistdaru Danesh Co.

This medicine has been prescribed for you only. Do not pass it on to others, even if their signs of illness are the same as yours.

This medicine could be prescribed by doctor for medical condition not mentioned in this leaflet.

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

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1. About Ziferon

Ziferon belongs to interferon family-group beta. Interferons are proteins produced in the body naturally to defense against the threatening infections by immune system.

2. Ziferon Packaging

1 Ziferon vial containing 9.6 million international unit (300 micrograms) interferon beta-1b, 1 pre-filled syringe with solvent, 1 sterile vial adapter, 2 alcohol pad and 1 short needle packed in a small box.

- After reconstitution, each milliliter contains 250 microgram (8.0 million IU) interferon beta-1b
- 15 small boxes, 1 patient leaflet and 1 injection card packed in a large box.

The other ingredients in the powder: mannitol and human albumin.

Each prefilled syringe contains 1.2 milliliter sodium chloride solution 0.54% w/v.

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3. Ziferon Indication

- Ziferon is used to treat relapsing forms of multiple sclerosis (MS) to reduce the number of flare-ups and slow down the development of physical disability associated with MS.

4. General consideration before using Ziferon

• Children

There have been no formal clinical trials undertaken in children.

Ziferon should not be used in these populations:

- **Allergic people** (hypersensitive) to natural or recombinant interferon beta, human albumin or any of the other ingredients of this medicine (mentioned in Ziferon Packaging).
- **People who currently suffer from severe depression and/or suicidal thoughts.**
- **People who have severe liver disease.**
- **Pregnant mothers:** You should not start treatment with this medicine.

Tell your doctor if any of the above applies to you.

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5. Pregnant & Lactating mothers

A. Pregnant mothers

- If you could get pregnant, use appropriate contraception while you are on Ziferon.
- If you are pregnant or you think you may be, tell your doctor. Ziferon therapy should not be started if you are pregnant.
- If you wish to become pregnant, discuss this with your doctor first.
- If you become pregnant while using Ziferon, stop your treatment and contact your doctor immediately.
- Your doctor will decide together with you, if your Ziferon treatment will be continued or not.

B. Lactating mothers

- It is not known whether interferon beta-1b passes into human breast milk. Your doctor decides whether to stop breast-feeding or to stop using the medicine.

Talk to your doctor before you start using Ziferon:

- If you have immune system problems.

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- If you have had depression or you are depressed or you have previously had thoughts of suicide.

Your doctor will closely monitor you during treatment.

- If your depression and/or suicidal thoughts are severe, you will not be prescribed Ziferon.
- If you have ever had seizures or if you are taking medicines to treat epilepsy, your doctor will monitor your treatment carefully.
- If you have severe kidney problems your doctor may monitor your kidney function during treatment. If you notice foam forming when you urinate, swelling in ankles or eyelids, rapid weight gain; call your doctor to follow the signs.

Call your doctor, if you experienced the followings:

- If you experience symptoms such as itching all over your body, swelling of your face and/or your tongue or sudden shortness of breath. These may be symptoms of a serious allergic reaction (hypersensitivity), which may become life threatening.
- If you feel noticeably more sad or hopeless than before the treatment with the medicine, or if you develop thoughts of suicide. If you become depressed while you are on Ziferon, you may need special treatment and your doctor will closely monitor you and may also consider stopping your

treatment. If you suffer from severe depression and/or suicidal thoughts, you will not be treated with interferon family.

- If you notice any unusual bruising, excessive bleeding after injury or if you seem to be catching a lot of infections. These may be symptoms of a fall in your blood cell count or in the number of platelets in your blood (cells, which help the blood to clot). Your doctor will monitor your treatment carefully.
- If you have loss of appetite, fatigue, feeling sick, repeated vomiting, nausea, especially, if you notice widespread itching, yellowing of the skin or of the whites of the eyes, or easy bruising. These symptoms may suggest problems with your liver. The most serious liver problems were reported in patients taking other medicines or who were suffering from diseases that can affect the liver (e.g. alcohol abuse, severe infection).
- If you experience symptoms like irregular heartbeat, swelling such as of the ankles or legs, or shortness of breath. This may suggest a disease of the heart muscle. If you have had history of heart problems, inform your doctor.
- If you notice pain in your belly which is radiating to your back, and/or you feel sick or have a fever. This may suggest an inflammation of the pancreas (pancreatitis).

6. Precautions

1. Your doctor prescribes diagnostic laboratory tests before starting

Ziferon and regularly during the treatment to assess your health condition. Also, she or he monitor your blood pressure, kidney function, etc.

2. Read all of this leaflet carefully before you start using this medicine and refer to the instructional centers.
3. If anyone else helps you for preparing the medicine and injection, she or he should refer to instructional centers.
4. It is preferred to inject Ziferon at evenings.
5. It is preferred to keep out the medicine 1 hour before injection of the refrigerator. Cool medicine can cause getting injection site reactions.
6. Do not reuse your syringe and short needle.
7. Ziferon is a Prescribed Only Medicine (POM).
8. Ziferon has no preservative and should be used immediately after preparation. Dispose any unused portion of the medicine.
9. Keep Ziferon out of sight and reach of the children.
10. Do not store the expired medicine and the unused.
11. Ziferon may cause drowsiness. If you are especially sensitive, this might

affect your ability to drive or use machines.

7. Ziferon & other medicines

- Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.
- No formal interaction studies have been carried out to find out whether Ziferon affects other medicines or is affected by them.
- Using this medicine with other medicines that modify the immune system response is not recommended, except anti-inflammatory medicines called corticosteroids or the adrenocorticotrophic hormone (ACTH).
- Ziferon should be used with caution with medicines which need liver function for their removal from the body, for example medicines used to treat epilepsy (like phenytoin) and medicines which affect the production of blood cells.

Ziferon with food and drink

Ziferon is injected under the skin, so any food or drink you consume is not thought to have any effect on the medicine.

8. Dosage & Administration

Always use this medicine exactly as your doctor has told you for more effective treatment.

The recommended dose for sub-cutaneous (under the skin) injection in MS patients is:

- Adults - Generally, 250 microgram (1.0 milliliter) every other day. (See the table below for dose titration).
- Efficacy and safety of the medicine has not been investigated in children and adolescents less than 18 years of age in comparison to others.

• **Important note:**

When starting treatment with Ziferon even you have had history usage of interferon beta-1b manufactured by another company, the following table for dose titration is recommended:

week of use	Recommended Titration	Dose (microgram)	Volume (milliliter)
Weeks 1-2	25%	62.5	0.25
Weeks 3-4	50%	125	0.50
Weeks 5-6	75%	187.5	0.75
Weeks 7+	100%	250	1

9. If you forget to use Ziferon

If you have forgotten to give yourself an injection at the right time, do it as soon as you remember and then follow on with the next one 48 hours later. It is preferred to inject Ziferon at a regular time for example at evenings.

Note: You are not permitted to stop treatment without your doctor order.

- Inform your doctor if you injected too much the medicine or injected it too often.

10. How to use Ziferon

Study the procedure described below carefully and pay attention to the notices before injection:

- Prepare everything you may need in injection procedure.
- Wash your hands with a soap and water thoroughly. Do not touch your hair and skin afterwards.
- Do not touch the short needle to keep it sterile during preparation procedure.

Proper preparing procedure

1. Take out the Ziferon kit from refrigerator. Leave it for 1 hour until reaches the room temperature. This will decrease pain in the injection site.



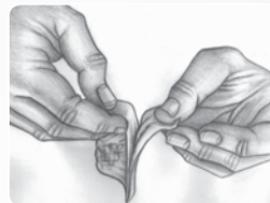
2. Remove the protective cap from the Ziferon vial. Do not touch top of the vial after removing the cap.



3. Use an alcohol pad to clean the top of the vial. Move in one direction and then leave the alcohol pad on top of the vial until you are ready to use it.



4. Open the pack containing the adapter, but leave the adapter inside. Do not remove or touch the adapter to keep it sterile.



5. Remove the alcohol pad from the top of the Ziferon vial. Place the pack containing the adapter on top of the vial. Push it down until it snaps into place. **Make sure of snapping into place with pushing it down again. If you do not perform this step properly, leakage can occur and you may lose your medicine.**



6. Pick up the prefilled syringe from the box and untwist it by turning the plastic cap. (Syringe tip should not touch the surrounding).

7. Remove the package from the adapter.

8. Keep the adapter by your thumb and forefinger and twist the syringe on the adapter by your other hand. Make sure that the syringe stays firmly on the adapter.



9. Transfer the prefilled syringe content completely (1.2 ml) into the vial.



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10. Keeping the syringe attached to the vial, gently swirl the vial (8 shape) until all powder has dissolved. Avoid shaking the vial vigorously, as this will produce foam. Extra foam can reduce efficacy of the medicine. After reconstitution, there will be 250 micrograms per milliliter solution of interferon beta-1b and can be kept in refrigerator for 3 hours.



Note: Wait a while until the produced foam disappears. This can prevent loss of efficacy caused by foam forming and reduce pain in injection site.

11. After reconstitution, Ziferon is clear, colorless to light yellow. Do not inject the vial content and discard the vial if the solution appears cloudy, or if floating particles are visible.

12. Turn the vial- adapter- syringe upside down. Slowly pull back the plunger rod of the syringe to draw up the vial content.



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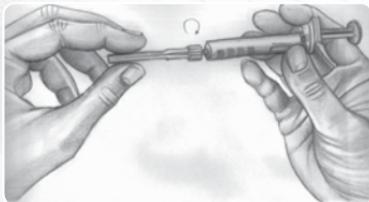
13. Tap the syringe gently until any air bubbles that formed rise to the top of the barrel of the syringe. Push the plunger rod down gently to empty the bubbles.

14. Push the plunger rod down slowly to the required volume (printed digits on the syringe body) as directed by your doctor.

15. Open the package containing a short needle, but leave its guard in place.

16. Keep the adapter by your thumb and forefinger and untwist the syringe counterclockwise by other hand protecting its tip from touching the surrounding.

17. Twist the short needle to the syringe immediately, by turning the guard once. Make sure that short needle stays on the syringe firmly.



18. Set the syringe aside until the injection site is prepared.

11. Proper injection guide

- Select an injection site as directed by your doctor and considering Ziferon injection card.

There are 8 zone for injection as below:

Arms (2 areas), abdomen (2 areas), buttocks (2 areas), thighs (2 areas). Each area consists of 6 sections: upper (right & left), median (right & left), lower (right & left). See Ziferon Injection Card for details.

Note: You may experience injection site reactions when using the medicine. This can include swelling, discoloration, inflammation, and pain or hypersensitivity reaction at the injection site.

12. Useful tips to reduce the risk of getting injection site reactions

- Compliance to useful tips in the (proper preparing procedure) section (called sterile procedure) plays an important role in reducing injection site reaction.
- Take out the Ziferon kit from refrigerator. Leave it for 1 hour until reaches the room temperature. This will decrease pain in the injection site.
- Change the injection site in every new injection. Do not inject in the

same section in 2 consecutive injections.

- Fill the Ziferon Injection card after each injection and make sure for compliance with the schedule in the card.
- Do not inject in area where you can feel lumps, bumps, firm knots, and pain.
- Do not inject in the skin that is discolored, indented, scabbed, or broken. Talk to your doctor about these or any other unusual conditions you may find.

Note: Consult your doctor in case of cracks in the skin or liquid coming out from the injection site.

- To reduce reaction at the injection site, your initial injections must be done in the presence of specialized nurses for Ziferon who have the necessary information and skills. (Study steps mentioned in the section <proper injection under the skin>).
- Use a cold compress few minutes before and after the injection. It can help to relieve and reduce pain at injection site.
- You must consult your doctor or specialized nurse for Ziferon, if injection site reactions or other side effects continue.
- The following tips are necessary for proper injection under the skin:

1. Clean and disinfect the chosen site for injection with an alcohol pad in one direction and wait until dry. Hold the syringe containing the prescribed dose like a pencil or dart. Remove the guard from the short needle, but do not touch the needle itself.

2. Gently pinch the skin together around the site, to lift it up a bit. This is necessary for proper injection under the skin.

3. Stick the straight into the skin at a 90 degrees angle with a quick, firm motion.

4. Using the slow steady push, inject the medicine by pushing the plunger rod all the way in until the syringe is empty.

5. After injection, wait 15 seconds and remove the needle by pulling straight out.

6. To prevent needle stick injury and spread of infection, do not try to recap the needle.

7. Place used needles, syringes, vials and alcohol pads in a closeable, puncture-resistant container such as special containers for hospital wastes, plastic bottles and an empty coffee can.



13. Adverse effects

Along with its needed effects, a medicine may cause some unwanted effects.

More Common (1 out of 10 patient)	Less Common (10 out of 100 patient)	Rare (1 out of 1000 patient)
<ul style="list-style-type: none">• Flu-like symptom complex including fever, chills, arthralgia, malaise, sweating, headache, or myalgia.• Injection site reactions including Redness, swelling, discoloration, inflammation, pain, hypersensitivity and necrosis in rare cases.• Gastrointestinal symptoms	<ul style="list-style-type: none">• Anemia (red blood cell count reduction)• Thyroid function changes• Menstrual disorders• Weight changes• Urticaria• Pruritus• Alopecia	<ul style="list-style-type: none">• Hypersensitivity reactions• Pancreatitis• Blood clots in the small blood vessels

Note: If you get any serious side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

At the beginning of treatment adverse reactions are common but they usually will be tolerate with further treatment and do not need any medical attention. Your doctor will tell you some recommendations to minimize common adverse effects.

Flu-like symptoms and injection site reactions are both common adverse effects at the start of Ziferon treatment but they usually decrease or go away over time. In general, they usually do not need any medical attention and subside with more Ziferon administration.

Some points to reduce common adverse effects (Flu-like symptoms):

- Consider injecting Ziferon at bed or use of analgesics and/or antipyretics before or after Ziferon administration (according to your doctor recommendations) may be helpful to diminish Flu-like symptoms.
- Gradual dose titration according to titration table at the beginning of treatment (in Dosage & Administration section 8) may be reduced Flu-like symptoms.

14. Storage of Ziferon

- Keep Ziferon in a refrigerator (2 to 8 degrees of centigrade).

- Do not freeze.
- After adding of solvent to Ziferon powder, you can keep the prepared solution for use for 3 hours in a refrigerator.
- Ziferon has no preservative and should be used immediately after preparation. (Single use only)
- After preparation, your solution is transparent (colorless to light yellow). Do not inject and discard the vial if the solution appears cloudy, or if floating particles are visible.

Last Revision for this package leaflet: September 2016

For more information about Ziferon, please contact your doctor, pharmacist, or Medical Support Team of Zistdaru Danesh Co.

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References: 1. www.fda.gov, FDA Approved labeling Text for Interferon beta-1b

Revised: October 2012 Reference ID: 3220464

2. www.drugs.com, interferon beta-1b