

**PACKAGE LEAFLET**

## **Package leaflet: Information for the user**

### **Zarzio 30 MU/0.5 ml solution for injection or infusion in pre-filled syringe Zarzio 48 MU/0.5 ml solution for injection or infusion in pre-filled syringe Filgrastim**

**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, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet:**

1. What Zarzio is and what it is used for
2. What you need to know before you use Zarzio
3. How to use Zarzio
4. Possible side effects
5. How to store Zarzio
6. Contents of the pack and other information

#### **1. What Zarzio is and what it is used for**

Zarzio is a white blood cell growth factor (granulocyte colony stimulating factor) and belongs to a group of proteins called cytokines. Growth factors are proteins that are produced naturally in the body but they can also be made using biotechnology for use as a medicine. Zarzio works by encouraging the bone marrow to produce more white blood cells.

A reduction in the number of white blood cells (neutropenia) can occur for several reasons and makes your body less able to fight infection. Zarzio stimulates the bone marrow to produce new white cells quickly.

#### **Zarzio can be used:**

- to increase the number of white blood cells after treatment with chemotherapy to help prevent infections;
- to increase the number of white blood cells after a bone marrow transplant to help prevent infections;
- before high-dose chemotherapy to make the bone marrow produce more stem cells which can be collected and given back to you after your treatment. These can be taken from you or from a donor. The stem cells will then go back into the bone marrow and produce blood cells;
- to increase the number of white blood cells if you suffer from severe chronic neutropenia to help prevent infections;
- in patients with advanced HIV infection which will help reduce the risk of infections.

#### **2. What you need to know before you use Zarzio**

##### **Do not use Zarzio**

- if you are allergic to filgrastim or any of the other ingredients of this medicine (listed in section 6).

##### **Warnings and precautions**

Talk to your doctor, pharmacist or nurse before using Zarzio.

Take special care with Zarzio if you have ever had an allergic reaction to latex.

Please tell your doctor before starting treatment **if you have:**

- osteoporosis (bone disease);
- sickle cell anaemia as Zarzio may cause sickle cell crisis.

Please tell your doctor immediately during treatment with Zarzio, if you:

- get left upper belly (abdominal) pain, pain below the left rib cage or at the tip of your left shoulder [these may be symptoms of an enlarged spleen (splenomegaly), or possibly rupture of the spleen],
- notice unusual bleeding or bruising [these may be symptoms of a decrease in blood platelets (thrombocytopenia), with a reduced ability of your blood to clot].
- have sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing as these could be signs of a severe allergic reaction.

Inflammation of the aorta (the large blood vessel which transports blood from the heart to the body) has been reported rarely in cancer patients and healthy donors. The symptoms can include fever, abdominal pain, malaise, back pain and increased inflammatory markers. Tell your doctor if you experience these symptoms.

### **Loss of response to filgrastim**

If you experience a loss of response or failure to maintain a response with filgrastim treatment, your doctor will investigate the reasons why including whether you have developed antibodies which neutralise filgrastim's activity.

Your doctor may want to monitor you closely, see section 4 of the package leaflet.

If you are a patient with severe chronic neutropenia, you may be at risk of developing cancer of the blood (leukaemia, myelodysplastic syndrome [MDS]). You should talk to your doctor about your risks of developing cancers of the blood and what testing should be done. If you develop or are likely to develop cancers of the blood, you should not use Zarzio unless instructed by your doctor.

If you are a stem cell donor, you must be aged between 16 and 60 years.

### **Take special care with other products that stimulate white blood cells.**

Zarzio is one of a group of products that stimulate the production of white blood cells. Your healthcare professional should always record the exact product you are using.

### **Other medicines and Zarzio**

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

### **Pregnancy and breast-feeding**

Zarzio has not been tested in pregnant or breast-feeding women.

Zarzio is not recommended during pregnancy.

It is important to tell your doctor if you:

- are pregnant;
- think you may be pregnant; or
- are planning to have a baby.

If you become pregnant during Zarzio treatment, please inform your doctor.

Unless your doctor directs you otherwise, you must stop breast feeding if you use Zarzio

## **Driving and using machines**

Filgrastim may have a minor influence on the ability to drive and use machines. Dizziness may occur following the administration of filgrastim.

## **Zarzio contains sorbitol:**

Zarzio contains sorbitol (E420), if you have been told by your doctor that you have a reaction to some sugars, contact your doctor before taking this medicinal product.

## **3. How to use Zarzio**

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

### **How is Zarzio given and how much should I take?**

Zarzio is usually given as a daily injection into the tissue just under the skin (known as a subcutaneous injection). It can also be given as a daily slow injection into the vein (known as an intravenous infusion). The usual dose varies depending on your illness and weight. Your doctor will tell you how much Zarzio you should take.

Patients having a bone marrow transplant after chemotherapy:

You will normally receive your first dose of Zarzio at least 24 hours after your chemotherapy and at least 24 hours after receiving your bone marrow transplant.

You, or people caring for you, can be taught how to give subcutaneous injections so that you can continue your treatment at home. However, you should not attempt this unless you have been properly trained first by your health care provider.

### **How long will I have to take Zarzio?**

You will need to take Zarzio until your white blood cell count is normal. Regular blood tests will be taken to monitor the number of white blood cells in your body. Your doctor will tell you how long you will need to take Zarzio.

## **Use in children**

Zarzio is used to treat children who are receiving chemotherapy or who suffer from severe low white blood cell count (neutropenia). The dosing in children receiving chemotherapy is the same as for adults.

## **If you use more Zarzio than you should**

Do not increase the dose your doctor has given you. If you think you have injected more than you should, contact your doctor as soon as possible.

## **If you forget to use Zarzio**

If you have missed an injection, or injected too little, contact your doctor as soon as possible. Do not take a double dose to make up for any missed doses.

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

## **4. Possible side effects**

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

**Please tell your doctor immediately** during treatment:

- if you experience an allergic reaction including weakness, drop in blood pressure, difficulty breathing, swelling of the face (anaphylaxis), skin rash, itchy rash (urticaria), swelling of the face lips, mouth, tongue or throat (angioedema) and shortness of breath (dyspnoea).
- if you experience a cough, fever and difficulty breathing (dyspnoea) as this can be a sign of Acute Respiratory Distress Syndrome (ARDS).
- if you get left upper belly (abdominal) pain, pain below the left rib cage or pain at the tip of your shoulder as there may be a problem with your spleen [enlargement of the spleen (splenomegaly) or rupture of the spleen].
- if you have blood in your urine (haematuria). Your doctor may regularly test your urine if you experience this side effect or if protein is found in your urine (proteinuria).
- if you have any of the following or combination of the following side effects:
  - swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion.These could be symptoms of a rare (may affect up to 1 in 1,000 people) condition called “Capillary Leak Syndrome” which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.

A very frequent side effect of filgrastim use is pain in your muscles or bones (musculoskeletal pain), which can be helped by taking standard pain relief medicines (analgesics). In patients undergoing a stem cell or bone marrow transplant, Graft versus Host Disease (GvHD) may occur- this is a reaction of the donor cells against the patient receiving the transplant; signs and symptoms include rash on the palms of your hands or soles of your feet and ulcer and sores in your mouth, gut, liver, skin, or your eyes, lungs, vagina and joints.

**Very common side effects** (seen in more than 1 in 10 people who take Zarzio)

- decrease of platelets which reduces the ability of blood to clot (thrombocytopenia)
- low red blood cell count (anaemia)
- headache
- diarrhoea
- vomiting
- nausea
- unusual hair loss or thinning (alopecia)
- pain in your muscles or bones (musculoskeletal pain)
- tiredness (fatigue)
- soreness and swelling of the digestive tract lining which runs from the mouth to the anus (mucosal inflammation)
- raised body temperature (pyrexia)

**Common side effects** (seen in more than 1 in 100 people taking Zarzio)

- the presence in tissues of harmful bacteria and their toxins (sepsis)
- bronchitis
- upper respiratory tract infection
- urinary tract infection
- enlargement of the spleen (splenomegaly)
- decreased oxygen-carrying protein in red blood cells (haemoglobin decreased)
- decreased appetite
- increase of certain enzymes in the blood
- inability to sleep (insomnia)
- dizziness
- reduced sense of touch or sensation (hypoesthesia)
- abnormal sensation (paraesthesia)

- high blood pressure (hypertension)
- low blood pressure (hypotension)
- coughing up blood (haemoptysis)
- shortness of breath (dyspnoea)
- cough
- pain in your mouth and throat (oropharyngeal pain)
- nose bleeds (epistaxis)
- oral pain
- constipation
- enlargement of the liver (hepatomegaly)
- rash
- superficial reddening of the skin (erythema)
- muscle spasms
- pain when passing urine (dysuria)
- blood in the urine (haematuria)
- chest pain
- pain
- generalised weakness (asthenia)
- malaise
- accumulation of fluid causing swelling in tissues perfused by the peripheral vascular system (oedema peripheral)
- transfusion reaction

**Uncommon side effects** (seen in more than 1 in 1,000 people taking Zarzio)

- increase in white blood cells (leukocytosis)
- allergic reaction (hypersensitivity)
- rejection of transplanted bone marrow (graft versus host disease)
- excess of uric acid in the blood (hyperuricaemia)
- changes in blood chemistry
- liver damage caused by blocking of the small veins within the liver (Veno-occlusive disease)
- severe lung inflammation causing difficulty in breathing (acute respiratory distress syndrome)
- lungs do not function as they should, causing breathlessness (respiratory failure)
- swelling and/or fluid in the lungs (pulmonary oedema)
- bleeding from the lung (pulmonary haemorrhage)
- inflammation of the lungs (interstitial lung disease)
- abnormal x-rays of the lungs (lung infiltration)
- lack of absorption of oxygen in the lung (hypoxia)
- increase of certain enzymes-in the body
- flat or raised red bump on the skin (rash maculo-papular)
- disease which causes bones to become less dense, making them weaker, more brittle and likely to break (osteoporosis)
- excess protein in the urine (proteinuria)
- injection site reaction

**Rare side effects** (seen in more than 1 in 10,000 people taking Zarzio)

- rupture of the spleen
- severe pain in the bones, chest, gut or joints (sickle cell anaemia with crisis)
- sudden life-threatening allergic reaction (anaphylactic reaction)
- blood glucose decreased
- pain and swelling of the joints, similar to gout (pseudogout)
- a change in how your body regulates fluids within your body and may result in puffiness (fluid volume disturbances)

- swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness (capillary leak syndrome)
- inflammation of the aorta (the large blood vessel which transports blood from the heart to the body)
- inflammation of the blood vessels in the skin (cutaneous vasculitis)
- plum-coloured, raised, painful sores on the limbs and sometimes the face and neck with a fever (Sweets syndrome)
- bone density decreased
- worsening of rheumatoid arthritis
- acute inflammation of kidney (glomerulonephritis)
- unusual change in the urine

### **Reporting of side effects**

If you get any side effects, talk to your doctor, 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 Zarzio**

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 carton and on the syringe label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).

Keep the pre-filled syringe in the outer carton in order to protect from light. Accidental freezing will not harm Zarzio.

The syringe can be removed from the refrigerator and left at room temperature for a single period of maximum 72 hours (but not above 25°C). At the end of this period, the product should not be put back in the refrigerator and should be disposed of.

Do not use this medicine if you notice discolouration, cloudiness or particles, it should be a clear, colourless to slightly yellowish liquid.

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 protect the environment.

## **6. Contents of the pack and other information**

### **What Zarzio contains**

- The active substance is filgrastim.  
Zarzio 30 MU/0.5 ml solution for injection or infusion in pre-filled syringe: Each pre-filled syringe contains 30 MU filgrastim in 0.5 ml, corresponding to 60 MU/ml.  
Zarzio 48 MU/0.5 ml solution for injection or infusion in pre-filled syringe: Each pre-filled syringe contains 48 MU filgrastim in 0.5 ml, corresponding to 96 MU/ml
- The other ingredients are glutamic acid, sorbitol (E420), polysorbate 80, sodium hydroxide and water for injections.
- The needle cap of the syringe may contain dry rubber (latex).

### **What Zarzio looks like and contents of the pack**

Zarzio is a clear, colourless to slightly yellowish solution for injection or infusion in pre-filled syringe.

Zarzio is available in packs containing 1, 3, 5 or 10 pre-filled syringes with injection needle and with or without a needle safety guard.

Not all pack sizes may be marketed.

### Product Licence Holder

Novartis (Singapore) Pte  
Ltd 20 Pasir Panjang Road  
#10-25/28 Mapletree Business City  
Singapore 117439

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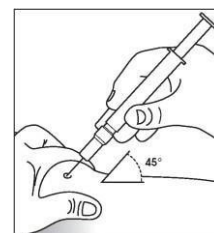
### Instructions on how to inject yourself

This section contains information on how to give yourself an injection of Zarzio. **It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse.** Zarzio is provided with or without a needle safety guard and you will be shown how to use this by your doctor or nurse. If you are not sure about giving the injection or you have any questions, please ask your doctor or nurse for help.

1. Wash your hands.
2. Remove one syringe from the pack and remove the protective cap from the injection needle. Syringes are embossed with graduation rings in order to enable partial use if required. Each graduation ring corresponds to a volume of 0.1 ml. If partial use of a syringe is required, remove unwanted solution before injection.
3. Clean the skin at the injection site using an alcohol wipe.
4. Form a skin fold by pinching the skin between thumb and forefinger.
5. Insert the needle into the skin fold with a quick, firm action. Inject the Zarzio solution as you have been shown by your doctor. You should check with your doctor or pharmacist if you are not sure.

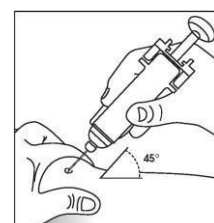
#### Pre-filled syringe without needle safety guard

6. Always keeping your skin pinched, depress the plunger slowly and evenly.
7. After injecting the liquid, remove the needle and let go of your skin.
8. Put the used syringe in the disposal container. Use each syringe only for one injection.



#### Pre-filled syringe with needle safety guard

6. Always keeping your skin pinched, depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. Do not release the pressure on the plunger!
7. After injecting the liquid, remove the needle while maintaining pressure on the plunger and then let go of your skin.



8. Let go of the plunger. The needle safety guard will rapidly move to cover the needle.
9. Discard any unused product or waste material. Only use each syringe for one injection.

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**The following information is intended for healthcare professionals only:**

The solution should be visually inspected prior to use. Only clear solutions without particles should be used. Accidental exposure to freezing temperatures does not adversely affect the stability of Zarzio.

Zarzio contains no preservative: In view of the possible risk of microbial contamination, Zarzio syringes are for single use only.

The needle cap of the syringe may contain dry rubber (latex), which should not be handled by persons sensitive to this substance.

Dilution prior to administration (optional)

If required, Zarzio may be diluted in glucose 50 mg/ml (5%) solution. Zarzio must not be diluted with sodium chloride solutions.

Dilution to a final concentration  $< 0.2$  MU/ml ( $2\text{ }\mu\text{g/ml}$ ) is not recommended at any time.

For patients treated with filgrastim diluted to concentrations  $< 1.5$  MU/ml ( $15\text{ }\mu\text{g/ml}$ ), human serum albumin (HSA) should be added to a final concentration of 2 mg/ml.

Example: In a final volume of 20 ml, total doses of filgrastim less than 30 MU ( $300\text{ }\mu\text{g}$ ) should be given with 0.2 ml of human serum albumin 200 mg/ml (20%) solution Ph. Eur. added.

When diluted in glucose 50 mg/ml (5%) solution, filgrastim is compatible with glass and a variety of plastics including polyvinylchloride, polyolefin (a copolymer of polypropylene and polyethylene) and polypropylene.

After dilution: Chemical and physical in-use stability of the diluted solution for infusion has been demonstrated for 24 hours at  $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$ . From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at  $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$ , unless dilution has taken place in controlled and validated aseptic conditions.

Using the pre-filled syringe with a needle safety guard

The needle safety guard covers the needle after injection to prevent needle stick injury. This does not affect normal operation of the syringe. Depress the plunger slowly and evenly until the entire dose has been given and the plunger cannot be depressed any further. While maintaining pressure on the plunger, remove the syringe from the patient. The needle safety guard will cover the needle when releasing the plunger.

Using the pre-filled syringe without a needle safety guard

Administer the dose as per standard protocol.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.