**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986**

This medicine is dispensed with a doctor's prescription only

# Binocrit 1,000 IU/0.5 ml
# Binocrit 2,000 IU/1 ml
# Binocrit 3,000 IU/0.3 ml
# Binocrit 4,000 IU/0.4 ml
# Binocrit 5,000 IU/0.5 ml
# Binocrit 6,000 IU/0.6 ml
# Binocrit 8,000 IU/0.8 ml
# Binocrit 10,000 IU/1 ml
# Binocrit 20,000 IU/0.5 ml
# Binocrit 30,000 IU/0.75 ml
# Binocrit 40,000 IU/1 ml

**Solution for injection in a pre-filled syringe**

***The active ingredient - epoetin alfa***

***Binocrit 1,000 IU/0.5 ml:***

One pre-filled syringe contains 0.5 ml solution for injection which contains 1,000 international units (IU) corresponding to 8.4 micrograms of epoetin alfa.

***Binocrit 2,000 IU/1 ml:***

One pre-filled syringe contains 1 ml solution for injection which contains 2,000 international units (IU) corresponding to 16.8 micrograms of epoetin alfa.

***Binocrit 3,000 IU/0.3 ml:***

One pre-filled syringe contains 0.3 ml solution for injection which contains 3,000 international units (IU) corresponding to 25.2 micrograms of epoetin alfa.

***Binocrit 4,000 IU/0.4 ml:***

One pre-filled syringe contains 0.4 ml solution for injection which contains 4,000 international units (IU) corresponding to 33.6 micrograms of epoetin alfa.

***Binocrit 5,000 IU/0.5 ml:***

One pre-filled syringe contains 0.5 ml solution for injection which contains 5,000 international units (IU) corresponding to 42.0 micrograms of epoetin alfa.

***Binocrit 6,000 IU/0.6 ml:***

One pre-filled syringe contains 0.6 ml solution for injection which contains 6,000 international units (IU) corresponding to 50.4 micrograms of epoetin alfa.

***Binocrit 8,000 IU/0.8 ml:***

One pre-filled syringe contains 0.8 ml solution for injection which contains 8,000 international units (IU) corresponding to 67.2 micrograms of epoetin alfa.

***Binocrit 10,000 IU/1 ml:***

One pre-filled syringe contains 1 ml solution for injection which contains 10,000 international units (IU) corresponding to 84.0 micrograms of epoetin alfa.

***Binocrit 20,000 IU/0.5 ml:***

One pre-filled syringe contains 0.5 ml solution for injection which contains 20,000 international units (IU) corresponding to 168.0 micrograms of epoetin alfa.

***Binocrit 30,000 IU/0.75 ml:***

One pre-filled syringe contains 0.75 ml solution for injection which contains 30,000 international units (IU) corresponding to 252.0 micrograms of epoetin alfa.

***Binocrit 40,000 IU/1 ml:***

One pre-filled syringe contains 1 ml solution for injection which contains 40,000 international units (IU) corresponding to 336.0 micrograms of epoetin alfa.

Inactive ingredients- see section 2 "Important information regarding some of the ingredients of the medicine" and section 6 "Further Information" in this leaflet.

**Read this leaflet carefully in its entirety before using this medicine:** This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.
This medicine has been prescribed for you. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

**For your attention, it is important you confirm that you always receive the same medicine prescribed for you by the attending specialist doctor, each time you receive the medicine in the pharmacy. If the medicine you received looks different from the one you usually get, or if the instructions for use have changed, please consult the pharmacist immediately and verify that you have received the right medicine. Any exchange or change in dosage of a medicine containing epoetin alfa (the active ingredient in the medicine) must be performed by the attending specialist doctor. Please check the brand name of the medicine prescribed for you in the prescription from the specialist doctor against the medicine you received from the pharmacist and make sure that they are identical.**

## 1. WHAT IS THIS MEDICINE INTENDED FOR?

- Treatment of symptomatic anemia associated with chronic renal failure (CRF):in adults and children aged 1 to 18 years who are on hemodialysis and adult patients who are on peritoneal dialysis;
  in adults with renal insufficiency not yet undergoing dialysis for the treatment of severe anemia of renal origin accompanied by clinical symptoms
- Treatment of adult patients receiving chemotherapy for solid tumors, malignant lymphoma, or multiple myeloma, who may need a transfusion as assessed by their general status (e.g. cardiovascular status, pre-existing anemia at the start of chemotherapy) for the treatment of anemia and reducing the need for transfusion.
- Treatment of anemia in adult patients who are in an autologous predonation program to increase the yield of autologous blood before major surgery. Treatment should only be given to patients with moderate anemia (hemoglobin concentration range between 10-13 g/dl (6.2-8.1 mmol/l), no iron deficiency), if blood saving procedures are not available or are insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males).
- For non iron deficient adult patients with anemia prior to major elective orthopedic surgery having a high risk for transfusion complications, to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anemia (hemoglobin concentration range between 10-13 g/dl or 6.2-8.1 mmol/l) who do not have an autologous predonation program available and with an expected blood loss of 900 to 1800 ml.

**Therapeutic group:** human erythropoietin produced in cell culture.
Binocrit stimulates the bone marrow to produce red blood cells.

## 2. BEFORE USING THE MEDICINE:

**Do not use this medicine if:**

- you are sensitive (allergic) to epoetin alfa or to any of this medicine's inactive ingredients listed in section 6.
- you have developed Pure Red Cell Aplasia (PRCA) (reduction or suppression of the red blood cell production) following treatment with erythropoietin of any type.
- you have high blood pressure not adequately controlled by medicinal treatment.
- you are about to have surgery, but you cannot receive proper treatment for the prevention of blood clot formation.
- you are due to undergo orthopedic surgery (e.g., of the hip or knee), and you have a severe heart disease, a severe disease in the arteries and veins, if you have recently had a heart attack or stroke, if you cannot take blood thinners.
- Do not use Binocrit to stimulate production of red blood cells (so that more blood can be taken from you) if you cannot receive infusions of your own blood during or after surgery.

**Special warnings regarding use of the medicine**

**Binocrit and other medicines that stimulate production of red blood cells may increase the risk of all patients to develop blood clots. The risk is higher if you have additional risk factors for development of blood clots (a blood clot in the past, if you are overweight, if you have diabetes, if you have a heart disease or if you are bedridden for a long period of time due to surgery or disease). Tell your doctor if one or more of the above conditions apply to you.**

**Before treatment with Binocrit, inform the doctor if you are suffering from:**

- Hypertension
- Epileptic fits or seizures
- Liver disease
- Anemia from other causes
- Porphyria (a rare blood disease)
- If you have cancer, note that medicines that stimulate production of red blood cells (such as Binocrit) may act as a growth factor and therefore may affect progression of your cancer. It may be preferable for you to receive a blood transfusion, depending on your individual status.
- If you have hepatitis C and you are being treated with interferon and ribavirin, you must discuss it with your doctor since combination of epoetin alfa with interferon and ribavirin led, in rare cases, to loss of the effect and to development of severe anemia due to depression of the manufacturing center of red blood cells in the bone marrow – Pure Red Cell Aplasia – PRCA. Binocrit is not intended for treatment of anemia associated with hepatitis C.
- If you are suffering from chronic kidney failure, especially if you are not responding well to treatment with Binocrit, your doctor will check your Binocrit dosage since a re-elevation of the dosage, if you are not responding to treatment, may increase the risk of heart or blood vessel problems and may increase the risk of heart attack, stroke and death.

If you are a cancer patient, be aware that Binocrit is associated with shorter survival and a higher death rate in head and neck, and metastatic breast cancer patients who are receiving chemotherapy.

Serious skin reactions including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported in association with epoetin treatment.

SJS/TEN can appear initially as a reddish rash, in the form of circular spots/macules, often with blisters on the trunk. Also, ulcers of mouth, throat, nose, genitals and eyes (red and swollen eyes) can occur.
These serious skin reactions may be associated with fever and/or other flu-like symptoms. The rash may get worse and spread and the skin will peel, resulting in a life-threatening condition.

If you develop a serious rash or another of these skin symptoms, stop taking Binocrit and contact your doctor or seek medical attention immediately (emergency room).

**Tests and follow-up**

Your doctor will monitor your blood pressure regularly while you are being treated with Binocrit.
If you are being treated with erythropoietin, check your blood hemoglobin values regularly, until they stabilize, and periodically check them after that. There is possibly increased risk of rare thromboembolic events (e.g., heart attacks, stroke, and pulmonary embolism) when hemoglobin levels rise beyond the target range.
Before starting treatment with Binocrit, take into account all other possible causes of anemia such as: iron deficiency, destruction of red blood cells (hemolysis), blood loss, vitamin $B_{12}$ or folic acid deficiency, and treat them.
The doctor may perform blood tests to decide if you need iron supplements to ensure an optimal response to Binocrit.
Your doctor may decide to perform routine blood tests to determine platelet counts in the blood during the first 8 weeks of treatment. There may be a slight dosage-dependent increase in the platelet count, within the normal range, during the course of treatment with Binocrit, that gradually decreases with continued treatment.
It is important to maintain normal iron levels in the blood throughout the course of treatment with Binocrit.
Your doctor may tell you to take iron tablets.

**Other medicines and Binocrit**

**If you are taking, or have recently taken, other medicines, including non-prescription medicines and dietary supplements, inform the doctor or pharmacist.** Particularly if you are taking:

- interferon together with ribavirin; cyclosporine, iron supplements, and blood cell stimulants.

**Pregnancy and breastfeeding**

It is very important to consult the doctor if you are pregnant, think you are pregnant, are planning to become pregnant, or are breastfeeding.

**Important information regarding some of the ingredients of the medicine:**

The product contains a negligible amount of sodium (less than 1 millimole / 23 milligrams in a dose) and is defined as "sodium free".

## 3. HOW SHOULD YOU USE THE MEDICINE?

Always use this medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
The dosage and treatment regimen will be determined by the doctor only.
Use this medicine at set intervals, as determined by your doctor.
**Do not exceed the recommended dose.**

**Binocrit can be injected in two ways:**
**1. either into a vein (intravenously)**
**2. or under the skin (subcutaneously).**
Your doctor will decide how it will be injected. In most cases it will be injected by a doctor, nurse, or other healthcare professional.
Binocrit may be self-injected subcutaneously only after appropriate training by a doctor or a nurse.
Do not inject Binocrit in the following cases:

- after the product's expiry date
- if you know or if you think that the product was accidentally frozen
- if there has been a failure in the refrigerator where the product is stored.

The dose of Binocrit you receive is based on your body weight in kilograms. The cause of your anemia may also be a factor in your doctor's decision about the dose.

**Instructions for subcutaneous injection**

When treatment starts, Binocrit is usually injected by a doctor or a nurse. Later, your doctor may suggest that you or your caregiver learn how to inject Binocrit under the skin yourself.

- **Do not try to inject yourself unless you have been trained by a doctor or nurse. If you are not sure how to inject the product or if you have any questions, ask your doctor for help.**
- **Use Binocrit exactly as instructed by your doctor.**
- **Make sure that you only inject the amount of liquid instructed by your doctor or nurse.**
- **Only use Binocrit if it has been stored correctly (see details in section 5, "How should the medicine be stored").**
- **Before use, take the Binocrit syringe out of the refrigerator and let it reach room temperature before injecting. This usually takes between 15 and 30 minutes. Use the syringe within 3 days of taking it out of the refrigerator.**

**Inject only one dose of Binocrit from each syringe.**

When Binocrit is injected subcutaneously, the dose injected is usually not more than 1 ml in a single injection site.
Binocrit is given alone and not mixed with other liquids for injection.
Do not shake Binocrit syringes. Prolonged vigorous shaking may damage the product. If you know that the syringe has been shaken, do not use that syringe.

Detailed instructions on how to inject yourself with Binocrit can be found at the end of this leaflet.

**If you accidentally used a high dose**

Tell your doctor or nurse immediately. Side effects from an overdose of Binocrit are unlikely. If you have taken an overdose or if a child accidentally swallowed the medicine, immediately refer to a doctor or proceed to a hospital emergency room, and bring the medicine package with you.

**If you forgot to inject this medicine**

As a rule, make the next injection as soon as you remember. If you are within a day of your next injection, do not inject when you remembered the missed dose. Wait and inject according to your normal schedule. Never inject two doses together!
Adhere to the treatment regimen as recommended by the doctor. Even if there is an improvement in your health, do not discontinue treatment with the medicine without consulting the doctor.

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

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

## 4. SIDE EFFECTS

As with any medicine, use of Binocrit 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.
Tell your doctor or nurse immediately if you experience any of the side effects listed below.

**Very common side effects (affect more than 1 in 10 patients):**

Diarrhea, vomiting, nausea, fever.
Respiratory tract congestion, such as nasal congestion and sore throat, has been reported by kidney patients who have not yet undergone dialysis.

**Common side effects (affect 1-10 in 100 patients):**

Increased blood pressure. Headaches, especially sudden, stabbing and migraine-like. Confused feeling or seizures may be signs of a sudden increase in blood pressure. This requires immediate treatment. There may be a need to treat a rise in blood pressure with additional medicines (or change in the medicines you are already taking for hypertension).
Blood clots (including deep vein thromboses and embolisms) may require emergency treatment. You may experience chest pain, shortness of breath and painful and red swelling of the leg.
Cough.
Skin rashes, which may be the result of an allergic reaction.
Bone or muscle aches.
Flu-like symptoms, such as headache, joint pains, sense of weakness, chills, fatigue and dizziness. These symptoms may be more common at the beginning of treatment. If you experience these symptoms upon injection into the vein, a slower injection may help reduce them in the future.
Redness, sensation of burning and pain at the injection site.
Swelling of the ankles, legs or fingers.
Arm or leg pain.

**Uncommon side effects (affect up to 1 in 100 patients):**

High blood potassium levels which may cause heart rate disturbances (this effect is very common in dialysis patients).
Epileptic fits.
Congestion of the nose or airways.
Allergic reaction.
Hives.

**Rare side effects (affect up to 1 in 1,000 patients):**

Severe and sudden anemia as a result of depression of the manufacturing center of red blood cells in the bone marrow (Pure Red Cell Aplasia – PRCA). The symptoms of this condition are: abnormal fatigue, spinning sensation and shortness of breath.
PRCA has been reported in very rare cases primarily in patients with kidney disease who were treated for months or years with epoetin alfa and other medicines that stimulate red blood cell production.
Increased blood platelet levels, normally involved in production of blood clots, may occur, especially at the beginning of treatment. The doctor will check for this.
Severe allergic reaction that may include: swollen face, lips, mouth, tongue or throat; difficulty swallowing or breathing; itchy rash (hives).
Problem with the blood that may cause pain, dark colored urine or increased sensitivity of the skin to sunlight (porphyria).

If you are undergoing hemodialysis treatments:

- Blood clots may form in the dialysis shunt. This may occur more often if you have low blood pressure or if you have fistula complications.
- Blood clots may form in your hemodialysis system. The doctor will decide if the heparin dosage should be increased during the dialysis.

Serious skin reactions including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have been reported in association with epoetin treatment. These can appear as reddish macules or circular patches often with blisters on the trunk, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. The syndrome may be accompanied by fever or flu-like symptoms.
**If you develop these symptoms, stop taking Binocrit and contact your doctor or seek medical attention immediately (emergency room).**

**If you experience any side effect, if any of the side effects worsen, or if you experience a side effect not mentioned in this leaflet, consult the doctor.**

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

## 5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine and any other medicine 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 explicit instruction from the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.

**Storage conditions:**

- Store in a refrigerator at a temperature between 2-8°C; do not freeze or shake.
  Keep the syringe in its original package in order to protect from light.
  The product can be taken out of the refrigerator and kept at room temperature (up to 25°C) for no more than 3 days. Once the syringe has been taken out of the refrigerator and has reached room temperature (up to 25°C), use it within 3 days or discard it.

Do not use the product:

- if the solution is cloudy or has particles in it
- if the seal is broken
- if the solution was accidentally frozen or if there has been a refrigerator failure.

## 6. FURTHER INFORMATION

Inactive ingredients:
glycine, sodium chloride, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, polysorbate 80, hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment), and water for injections.

What the medicine looks like and the contents of the package - Binocrit is a clear, colorless solution in a pre-filled syringe. The syringes are wrapped in a blister.

License holder's name and address: Novartis Israel Ltd., P.O.Box 7126, Tel Aviv.

Manufacturer's name and address: Sandoz GmbH, Kundl, Austria.

This leaflet was reviewed and approved by the Ministry of Health in December 2018, and revised in April 2020 in accordance with Ministry of Health guidelines.

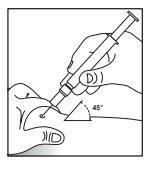
Registration number of the medicine in the National Drug Registry of the Ministry of Health: 1470833360, 1470933361,1471733370, 1471133363, 1471233364, 1471333365, 1471433366, 1471533367, 1471633368, 1471033362, 1471833372

**Instructions on how to inject yourself (for patients with symptomatic anemia caused by kidney disease, adult patients receiving chemotherapy, or adult patients with moderate anemia scheduled for major orthopedic surgery only)**

This section contains information on how to give yourself an injection of Binocrit. It is important that you do not try to give yourself the injection unless you have received special training from your doctor or nurse. Binocrit 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.

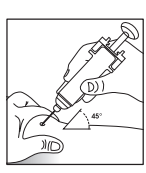
1. Wash your hands.
2. Remove one syringe from the pack and remove the protective cap from the injection needle. Syringes are embossed with graduation rings in order to enable partial use if required. Each graduation ring corresponds to a volume of 0.1 ml. If partial use of a syringe is required, remove 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 Binocrit solution as you have been shown by your doctor. You should check with your doctor or pharmacist if you are not sure how to do this.

***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. Apply pressure over the injection site with a dry, sterile pad.
8. Discard any unused product or waste material. Only use each syringe 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 only then let go of your skin. Apply pressure over the injection site with a dry, sterile pad.
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.