Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Bosulif® 100 mg
Bosulif® 400 mg
Bosulif® 500 mg
Film-coated tablets

Each tablet contains:
bosutinib (as monohydrate) 100 mg, 400 mg or 500 mg

Inactive ingredients and allergens: see section 2 under 'Important information about some of this medicine's ingredients' and section 6 "Further information".

Read the entire leaflet carefully before using this medicine. This leaflet contains concise information about this medicine. If you have further questions, consult your 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 to yours.

This medicine is not intended for children and adolescents under 18 years old.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Bosulif is intended for the treatment of adult patients with:

- newly-diagnosed chronic phase (CP) Philadelphia chromosome-positive chronic myelogenous leukaemia (Ph+ CML).
- chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) [TKI(s)] and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Therapeutic group:
protein kinase enzyme inhibitors.

2. BEFORE USING THIS MEDICINE

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient or to any of the other ingredients in this medicine(listed in section 6).
- You were told by your doctor that your liver has been damaged and is not working normally.

Special warnings regarding use of the medicine
Before treatment with Bosulif, tell the doctor if:

- **you have, or have had in the past, liver problems.** Tell your doctor if you have a history of liver problems including hepatitis (liver infection or inflammation) of any kind, or a history of any of the following signs and symptoms indicating liver problems such as: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor will send you to perform blood tests to check your liver function before you start treatment with Bosulif, during the first 3 months of treatment and as necessary later.
- **you have diarrhea and vomiting.** Tell your doctor if you develop any of the following signs and symptoms: an increase in the number of stools (bowel movements) per day over normal, an increase in episodes of vomiting, blood in your stool (bowel movements), urine, or vomit, or if you have black stools. If you are taking medicines to treat nausea and vomiting, particularly if these medicines contain domperidone, ask your doctor if they may increase the risk of heart rhythm disorders. Treating nausea or vomiting with such medicines together with Bosulif may result in a greater risk of dangerous heart rhythm disorders (arrhythmias).

- **you suffer from bleeding problems.** Tell your doctor if you develop any of the following signs and symptoms such as: bleeding or bruising without having an injury.

- **you have an infection.** Tell your doctor if you develop any of the following signs and symptoms such as: fever, problems with urinating such as burning when passing urine, a new sore throat, or a new cough.
- **you have fluid retention.** Tell your doctor if you develop any of the following signs and symptoms of fluid retention during Bosulif treatment such as: swelling of the ankles, feet or legs; shortness of breath, chest pain or a cough (these may be signs of fluid retention in the lungs or chest).
- **you have heart problems.** Tell your doctor if you have a heart disorder such as heart failure, arrhythmia or an abnormal electrical signal called prolongation of the QT interval. This is always important, but especially if you are experiencing frequent or prolonged diarrhea as described above. If you faint (loss of consciousness) or have an irregular heartbeat while taking Bosulif, contact the doctor immediately, as this may be a sign of a serious heart condition.
- **you have been told that you have kidney problems.** Tell the doctor if your urine is lighter in color and you are producing larger amounts of urine and urinating more frequently or if your urine is darker and you are urinating less frequently and producing smaller amounts of urine. Also tell your doctor if you are losing weight or have experienced swelling of the feet, ankles, legs, hands or face.
- **you have ever had or might now have a hepatitis B infection.** Bosulif could cause hepatitis B to become active again, which can be fatal in some cases. Patients must be carefully checked by the doctor for signs of this infection before starting treatment with the medicine.
- **you have or have had pancreas problems.** Tell the doctor if you have or if you develop abdominal pain or discomfort.
- **you have any of the following symptoms: serious skin rashes.** Tell your doctor if you develop any of the following signs and symptoms of painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membranes (e.g., mouth and lips).
- **you notice any of the following symptoms: pain in your side, blood in your urine or reduced amount of urine.** When your disease is very severe, your body may not be able to clear all the waste products from the dying cancer cells. This is called tumor lysis syndrome and can cause kidney failure and heart problems within 48 hours of the first dose of Bosulif. Your doctor will be aware of this and may ensure you are adequately hydrated and give you other medicines to help prevent it.

Sun/UV protection
You may become more sensitive to the sun or UV rays while taking bosutinib. It is important to cover sunlight-exposed areas of skin and use sunscreen with high sun protection factor (SPF).

Children and adolescents
Bosulif is not intended for children and adolescents under 18 years old. There is no information regarding the safety and effectiveness of using this preparation in children and adolescents.

Tests and follow-up
- Bosulif may cause liver problems. Your doctor will order blood tests to check your liver function before you start treatment with Bosulif, during the first 3 months of treatment, and as necessary later.
- Bosulif may cause low platelet count (thrombocytopenia), low red blood cell count (anemia), and low white blood cell count (neutropenia). The doctor will send you to perform regular blood tests every week during the first month of treatment and every month after that or as necessary.
- Bosulif may affect your heart rhythm. Your doctor may ask you to perform ECG tests before you start treatment and as necessary later.

Drug interactions
If you are taking or have recently taken, other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist.
Particularly if you are taking:
<u>The following active substances may increase the risk of side effects with Bosulif:</u>
- ketoconazole, itraconazole, voriconazole, posaconazole and fluconazole, used to treat fungal infections
- clarithromycin, telithromycin, erythromycin, and ciprofloxacin, used to treat bacterial infections
- nefazodone, used to treat depression
- mibefradil, diltiazem and verapamil, used to lower blood pressure in people with high blood pressure

- ritonavir, lopinavir/ritonavir, indinavir, nelfinavir, saquinavir, atazanavir, amprenavir, fosamprenavir and darunavir, used to treat human immunodeficiency virus (HIV)/AIDS
- boceprevir and telaprevir, used to treat hepatitis C
- aprepitant, used to treat and prevent nausea and vomiting
- imatinib, used to treat a type of leukemia (a blood cancer)
- crizotinib, used to treat a type of lung cancer called non-small cell lung cancer

The following active substances may reduce the effectiveness of Bosulif:
- rifampicin, used to treat tuberculosis
- phenytoin and carbamazepine, used to treat epilepsy
- bosentan, used to lower high blood pressure in the lungs (pulmonary artery hypertension)
- nafcillin, an antibiotic used to treat bacterial infections
- St. John's wort, a herbal remedy used to treat depression
- efavirenz and etravirine, used to treat human immunodeficiency virus (HIV)/AIDS (acquired immune deficiency syndrome)
- modafinil, used to treat certain types of sleep disorders

Avoid using these medicines during your treatment with Bosulif. If you are taking any of these medicines, tell the doctor. Your doctor may change the dose of these medicines, change the dose of Bosulif, or switch to a different medicine.

The following active substances may affect heart rhythm:
- amiodarone, disopyramide, procainamide, quinidine and sotalol used to treat heart problems
- chloroquine, halofantrine used to treat malaria
- clarithromycin and moxifloxacin, antibiotics used to treat bacterial infections
- haloperidol, used to treat psychotic disorders such as schizophrenia
- domperidone, used to treat nausea and vomiting or to stimulate breast milk production
- methadone, used to treat pain

These medicines should be taken with caution during your treatment with Bosulif. If you are taking any of these medicines, tell the doctor.

The medicines listed here may not be the only ones that could interact with Bosulif.

Using this medicine and food
Take this medicine with food.
Avoid grapefruit, grapefruit juice, or dietary supplements that contain grapefruit extract because they may increase the risk of side effects.

Pregnancy, breastfeeding and fertility
Do not take Bosulif during pregnancy, unless clearly necessary, because Bosulif could harm an unborn baby.
Ask your doctor for advice before taking Bosulif if you are pregnant or might become pregnant.

Women taking Bosulif are advised to use effective contraception during treatment and for at least one month after the last dose. Vomiting or diarrhea may reduce the effectiveness of oral contraceptives.

There is a risk that treatment with Bosulif will lead to decreased fertility. You may wish to seek advice about preserving fertility and/or sperm storage before the treatment starts.
If you are breastfeeding, tell the doctor. Do not breastfeed during treatment with Bosulif as it could harm your baby.

Driving and using machines
Using this medicine can make you feel dizzy, have blurred vision or feel unusually tired. If this happens to you, do not drive or operate machines until these side effects have gone away.

Important information about some of this medicine's ingredients

Bosulif contains sodium. This medicine contains less than 1 millimole (23 mg) of sodium per 100 mg, 400 mg, or 500 mg tablet, that is to say essentially 'sodium-free'.

3. HOW TO USE THIS MEDICINE?

Always use this medicine according to your doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the medicine.
The dosage and treatment regimen will be determined by your doctor only.

- **The standard dose is usually** 400 mg once a day for patients with newly-diagnosed chronic myelogenous leukaemia.
- **The standard dose is usually** 500 mg once a day for patients whose previous treatments for chronic myelogenous leukaemia have either not worked or were not suitable.

If you have kidney problems, the doctor may reduce your dosage. The doctor may adjust your dosage depending on your medical condition, your response to treatment, or any side effect you may experience.
Do not exceed the recommended dose.

Take this medicine once a day with food. Swallow the tablet whole with water.
Do not crush/split/chew the tablet because this is a film-coated tablet.

If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine at the scheduled time and less than 12 hours have passed, take your usual dose. If more than 12 hours have passed, take your next dose at the regular time on the following day. Do not take a double dose to make up for a missed dose.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

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

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Bosulif, may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Contact the doctor immediately if you experience any of the following serious side effects:

- **Blood disorders.** Contact the doctor immediately if you have any of the following symptoms: bleeding, easy bruising or fever, you might have blood or lymphatic system disorder.
- **Liver disorders.** Contact the doctor immediately if you have any of the following symptoms: itching, yellow eyes or skin, dark urine and pain or discomfort in the right upper stomach area or fever.
- **Stomach/intestinal disorders.** Tell the doctor if you develop heartburn, stomach pain, diarrhea, constipation, nausea and vomiting.
- **Heart problems.** Tell the doctor if you have a heart disorder, such as heart failure, heart rhythm disorders, or an abnormal electrical signal called prolongation of the QT interval, or if you lose consciousness (faint) while taking Bosulif. Tell your doctor immediately if you have any of the following symptoms: chest pain or pressure, pain in your arms, back, neck or jaw; shortness of breath; unexpected rapid weight gain, especially in the feet, ankles, legs and stomach.
- **Hepatitis B reactivation.** Recurrence (reactivation) of hepatitis B (a viral liver infection) if you have had hepatitis B in the past.
- **Serious skin reactions.** Tell the doctor immediately if you have any of the following symptoms: painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membranes (e.g. mouth and lips).

Additional side effects:
Very common side effects (may affect more than 1 in 10 people):
reduction in the number of platelets, red blood cells and/or neutrophils (a type of white blood cells), diarrhea, vomiting, stomach pain, nausea, fever, swelling of hands, feet or face, fatigue, weakness, respiratory tract

infection, nasopharyngitis, changes in blood tests that determine if Bosulif is affecting your kidneys, liver and/or pancreas, decreased appetite, joint pain, back pain, headache, skin rash that can be itchy or spread, cough, shortness of breath, feeling of instability (dizziness), fluid in the lungs (pleural effusion), itching.

Common side effects (may affect up to 1 in 10 people):
low white blood cells count (leukopenia), stomach inflammation, bleeding from the stomach or intestine, pain, chest pain, toxic damage to the liver, liver disorder including abnormal liver function, pneumonia, influenza, bronchitis, heart rhythm problems that cause fainting, dizziness and palpitations, increase in blood pressure, high level of potassium in the blood, low level of phosphorus in the blood, dehydration, muscle pain, alteration of the sense of taste, acute kidney failure, kidney failure, impaired kidney function, fluid around the heart (pericardial effusion), ringing in the ears (tinnitus), urticaria (hives), acne, photosensitivity reaction (sensitivity to UV rays from the sun and other light sources), allergic reaction, abnormally high blood pressure in the arteries of the lungs (pulmonary hypertension), acute inflammation of the pancreas (acute pancreatitis), respiratory failure.

Uncommon side effects (may affect up to 1 in 100 people):
fever associated with low white blood cell count (febrile neutropenia), damage to the liver, life-threatening allergic reaction (anaphylactic shock), acute pulmonary edema (build-up of fluid in the lungs), skin rash, significant decrease in number of granulocytes (a type of white blood cell), inflammation of the sac-like covering of the heart (pericarditis), severe skin disorder (erythema multiforme), tumour lysis syndrome: nausea, shortness of breath, irregular heartbeat, muscle cramps, seizures, clouding of urine and tiredness associated with abnormal test results (high potassium, uric acid and phosphorous levels and low calcium levels in the blood) that can lead to changes in kidney function and acute renal failure.

Side effects of unknown frequency (the frequency cannot be estimated from the available data):
severe skin disorder (Stevens-Johnson syndrome, toxic epidermal necrolysis) due to an allergic reaction, exfoliative (scaly, peeling) rash, interstitial lung disease (disorders causing scarring in the lungs): signs include cough, difficulty breathing, painful breathing.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report Side effects to the Ministry of Health by following the link “Reporting Side Effects of Drug Treatment” on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects or by using the link: https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

- Prevent poisoning! This and any other medicine should be kept in a closed place, out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

- No special storage conditions. Storing at room temperature is recommended.

6. FURTHER INFORMATION

In addition to the active ingredient, this medicine also contains:
microcrystalline cellulose, croscarmellose sodium, poloxamer 188, povidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, iron oxide yellow (in the 100 mg and 400 mg tablets) and iron oxide red (in the 500 mg and 400 mg tablets).

What the medicine looks like and contents of the pack:
Bosulif 100 mg: film-coated, yellow colored, oval biconvex tablets that are debossed with “Pfizer” on one side and “100” on the other side.
Bosulif 400 mg: film-coated, orange colored, oval biconvex tablets that are debossed with “Pfizer” on one side and “400” on the other side.

Bosulif 500 mg: film-coated, red colored, oval biconvex tablets that are debossed with “Pfizer” on one side and “500” on the other side.

The tablets are available in blister tray packages.

Registration holder and address: Pfizer Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725.

Registration number of the medicine in the Ministry of Health’s National Drug Registry:
Bosulif 100 mg: 152-88-34014
Bosulif 400 mg: 164-34-36062
Bosulif 500 mg: 152-89-34015

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