Package leaflet: Information for the user

Bosulif 100 mg film-coated tablets
Bosulif 400 mg film-coated tablets
Bosulif 500 mg film-coated tablets
bosutinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking 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 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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Bosulif is and what it is used for

Bosulif contains the active substance bosutinib. It is used to treat adult patients who have a type of leukaemia called Philadelphia chromosome-positive (Ph-positive) Chronic Myeloid Leukaemia (CML) and are newly-diagnosed or for whom previous medicines to treat CML have either not worked or are not suitable. Ph-positive CML is a cancer of the blood which makes the body produce too many of a specific type of white blood cell called granulocytes.

If you have any questions about how Bosulif works or why this medicine has been prescribed for you, ask your doctor.

2. What do you need to know before you take Bosulif

Do not take Bosulif
- if you are allergic to bosutinib or any of the other ingredients of this medicine (listed in section 6).
- if your doctor has told you that your liver has been damaged and is not working normally.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Bosulif:
- **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 of liver problems: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor should do blood tests

to check your liver function prior to your starting treatment with Bosulif and for the first 3 months of treatment with Bosulif, and as clinically indicated.

- **if you have diarrhoea 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 vomit, stools (bowel movements) or urine, or have black stools (tarry black bowel movements). You should ask your doctor if use of your treatment for vomiting may result in a greater risk of heart arrhythmias. In particular, you should ask your doctor if you want to use a medicine containing domperidone for the treatment of nausea and/or vomiting. Treatment of nausea or vomiting with such medicines together with Bosulif may result in a greater risk of dangerous heart arrhythmias.

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

- **if you have an infection.** Tell your doctor if you develop any of the following signs and symptoms such as fever, problems with urine such as burning on urination, a new cough, or a new sore throat.

- **if 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; difficulty breathing, chest pain or a cough (these may be signs of fluid retention in the lungs or chest).

- **if you have heart problems.** Tell your doctor if you have a heart disorder, such as arrhythmias or an abnormal electrical signal called "prolongation of the QT interval". This is always important, but especially if you are experiencing frequent or prolonged diarrhoea as described above. If you faint (loss of consciousness) or have an irregular heartbeat while taking Bosulif, tell your doctor immediately, as this may be a sign of a serious heart condition.

- **if you have been told that you have problems with your kidneys.** Tell your doctor if you are urinating more frequently and producing larger amounts of urine with a pale colour or if you are urinating less frequently and producing smaller amounts of urine with a dark colour. Also tell your doctor if you are losing weight or have experienced swelling of your feet, ankles, legs, hands or face.

- **if you have ever had or might now have a hepatitis B infection.** This is because Bosulif could cause hepatitis B to become active again, which can be fatal in some cases. Patients will be carefully checked by their doctor for signs of this infection before treatment is started.

- **if you have or have had pancreas problems.** Tell your doctor if you develop abdominal pain or discomfort.

- **if you have any of these 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 membrane (e.g., mouth and lips).

- **if you notice any of these 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 tumour 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.

Children and adolescents

Bosulif is not recommended for people whose age is under 18 years. This medicine has not been studied in children and adolescents.

Other medicines and Bosulif
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, vitamins, and herbal medicines. Some medicines can affect the levels of Bosulif in your body. You should inform your doctor if you are taking medicines containing active substances such as those listed below:

The following active substances may increase the risk of side effects with Bosulif:
- 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 prevent and control nausea (feeling sick) and vomiting.
- imatinib, used to treat a type of leukaemia.
- 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 preparation obtained without a prescription), used to treat depression.
- efavirenz and etravirine, used to treat HIV infections/AIDS.
- modafinil, used to treat certain types of sleep disorders.

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

The following active substances may affect the heart rhythm:
- amiodarone, disopyramide, procainamide, quinidine and sotalol used to treat heart disorder.
- chloroquine, halofantrine used to treat malaria.
- clarithromycin and moxifloxacin antibiotics used to treat bacterial infections.
- haloperidol, used to treat psychotic disease 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 them, tell your doctor.

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

Bosulif with food and drink
Do not take Bosulif with grapefruit or grapefruit juice, as it may increase the risk of side effects.

Pregnancy, breast-feeding and fertility
Bosulif is not to be used 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 will be advised to use effective contraception during treatment and for at least 1 month after the last dose. Vomiting or diarrhoea may reduce the effectiveness of oral contraceptives.

There is a risk that treatment with Bosulif will lead to decreased fertility and you may wish to seek advice about sperm storage before the treatment starts.

If you are breast-feeding, tell your doctor. Do not breast-feed during treatment with Bosulif as it could harm your baby.

Driving and using machines
If you experience dizziness, have blurred vision or feel unusually tired, do not drive or operate machines until these side effects have gone away.

3. How to take Bosulif

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

Bosulif will only be prescribed to you by a doctor with experience in medicines to treat leukaemia.

Dose and method of administration
The recommended dose is 400 mg once daily for patients with newly-diagnosed CML. The recommended dose is 500 mg once daily for patients whose previous medicines to treat CML have either not worked or are not suitable. In the event that you have moderate or severe kidney problems, your doctor will reduce your dose by 100 mg once daily for moderate kidney problems and by an additional 100 mg once daily for severe kidney problems. Your doctor may adjust the dose using the 100 mg tablets depending upon your medical conditions, upon your response to treatment and/or on any side effect you may experience. Take the tablet(s) in the morning with food. Swallow the tablet(s) whole with water.

If you take more Bosulif than you should
If you accidentally take too many Bosulif tablets or a higher dose than you need, contact a doctor for advice right away. If possible, show the doctor the pack, or this leaflet. You may require medical attention.

If you forget to take Bosulif
If dose is missed by less than 12 hours, take your recommended dose. If a dose is missed by more than 12 hours, take your next dose at your regular time on the following day.
Do not take a double dose to make up for the forgotten tablets.

If you stop taking Bosulif
Do not stop taking Bosulif unless your doctor tells you to do so. If you are not able to take the medicine as your doctor prescribed or you feel you do not need it anymore, contact your doctor right away.

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

4. Possible side effects

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

You must immediately contact your doctor if you experience any of those serious side effects (see also section 2 “What you need to know before you take Bosulif”):

Blood disorders. Tell your doctor right away if you have any of these symptoms: bleeding, fever or easy bruising (you might have blood or lymphatic system disorder).

Liver disorders. Tell your doctor right away if you have any of these symptoms: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area or fever.

Stomach/intestinal disorders. Tell your doctor if you develop stomach pain, heartburn, diarrhoea, constipation, nausea and vomiting.

Heart problems. Tell your doctor if you have a heart disorder, such as an abnormal electrical signal called "prolongation of the QT interval", or if you faint (loss of consciousness) or have an irregular heart beat while taking Bosulif.

Hepatitis B reactivation. Recurrence (reactivation) of hepatitis B infection when you have had hepatitis B in the past (a liver infection).

Severe skin reactions. Tell your doctor right away if you have any of these symptoms: painful red or purplish rash that spreads and blisters and/or other lesions begin to appear in the mucous membrane (e.g. mouth and lips).

Side effects with Bosulif may include:

Very common side effects (may affect more than 1 in 10 people):
- reduction in the number of platelets, red blood cells and/or neutrophils (type of white blood cells).
- diarrhoea, vomiting, stomach pain, nausea.
- fever, swelling of hands, feet or face, fatigue, weakness.
- respiratory tract infection.
- nasopharyngitis.
- changes in blood test to determine if Bosulif is affecting your liver and/or pancreas.
- decrease of appetite.
- joint pain, back pain.
- headache.
- skin rash, which may be itchy and/or generalised.
- cough.
- shortness of breath.

Common side effects (may affect up to 1 in 10 people):
- low white blood cells count (leukopenia).
- stomach irritation (gastritis), bleeding from the stomach or intestine.
- chest pain, pain.
- toxic damage to the liver, abnormal hepatic function including liver disorder.
- infection of the lung (pneumonia), influenza, bronchitis.
- defect in cardiac rhythm that predisposes to fainting, dizziness and palpitation.
- increase in blood pressure.
- high level of potassium in the blood, low level of phosphorus in the blood, excessive loss of body fluid (dehydration).
- pain in the muscles.
- feeling of instability (dizziness), alteration of the sense of taste (dysgeusia).
- acute kidney failure, kidney failure, kidney impairment.
- fluid on the lungs (pleural effusion).
- fluid around the heart (pericardial effusion).
- ringing in the ears (tinnitus).
- itching, urticaria (hives), acne.

Uncommon side effects (may affect up to 1 in 100 people):
- fever associated with low white blood cell count (febrile neutropenia).

- acute inflammation of the pancreas (acute pancreatitis).
- damage to the liver.
- life-threatening allergic reaction (anaphylactic shock).
- abnormal build-up of fluid in the lungs (acute pulmonary oedema).
- respiratory failure.
- allergic reaction.
- abnormally high blood pressure in the arteries of the lungs (pulmonary hypertension).
- skin eruption.
- inflammation of the sac-like covering of the heart (pericarditis).
- a marked decrease in the number of granulocytes (a type of white blood cells).

Rare side effects (may affect up to 1 in 1,000 people):
- severe skin disorder (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) due to an allergic reaction, exfoliative (scaly, peeling) rash.

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 (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Ireland:
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971;
Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

United Kingdom:
Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store

Malta:
ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

5. How to store Bosulif

- 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 blister foil and carton after "EXP". The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.
- 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. Content of the pack and other information

What Bosulif contains
- The active substance is bosutinib. Bosulif film-coated tablets come in different strengths.
  Bosulif 100 mg: each film-coated tablet contains 100 mg bosutinib (as monohydrate).
  Bosulif 400 mg: each film-coated tablet contains 400 mg bosutinib (as monohydrate).
  Bosulif 500 mg: each film-coated tablet contains 500 mg bosutinib (as monohydrate).

- The other ingredients are: microcrystalline cellulose (E460), croscarmellose sodium (E468), poloxamer 188, povidone (E1201) and magnesium stearate (E470b). The tablet film-coating contains polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc (E553b) and iron oxide yellow (E172, for Bosulif 100 mg and 400 mg) or iron oxide red (E172, for Bosulif 400 mg and 500 mg).

What Bosulif looks like and contents of the pack

Bosulif 100 mg film-coated tablets are yellow, oval biconvex, debossed with “Pfizer” on one side and “100” on the other side.
Bosulif 100 mg is available in blisters containing either 14 or 15 film-coated tablets in cartons of 28 or 30 film-coated tablets or 112 film-coated tablets.

Bosulif 400 mg film-coated tablets are orange, oval biconvex, debossed with “Pfizer” on one side and “400” on the other side.
Bosulif 400 mg is available in blisters containing either 14 or 15 film-coated tablets in cartons of 28 or 30 film-coated tablets.

Bosulif 500 mg film-coated tablets are red, oval biconvex, debossed with “Pfizer” on one side and “500” on the other side.
Bosulif 500 mg is available in blisters containing either 14 or 15 film-coated tablets in cartons of 28 or 30 film-coated tablets.

Not all pack sizes may be marketed.

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Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer
Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This medicine has been given “conditional approval”.
This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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