PACKAGE LEAFLET

Package leaflet: Information for the patient

Bosutinib Rowex 100 mg film-coated tablets
Bosutinib Rowex 400 mg film-coated tablets
Bosutinib Rowex 500 mg film-coated tablets

bosutinib

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 Bosutinib Rowex is and what it is used for

Bosutinib Rowex contains the active substance bosutinib. It is used to treat adult and paediatric patients aged 6 years and older who have a type of leukaemia called chronic phase (CP) 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. It is also used to treat adult patients with accelerated phase (AP) and blast phase (BP) Ph+ CML for whom previous medicines to treat CML have not worked or are not suitable.

In patients with Ph-positive CML a change in DNA (genetic material) triggers a signal that tells the body to produce too many of a specific type of white blood cell called granulocytes. This medicine blocks this signal and therefore stops the production of these cells.

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

2. What you need to know before you take Bosutinib Rowex

Do not take Bosutinib Rowex
- 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 Bosutinib Rowex:

- **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 signs and symptoms of liver problems (see section 4 ``Possible side effects``) because this medicine may affect your liver function. Your doctor should do blood tests to check your liver function prior to your starting treatment with Bosutinib Rowex and for the first 3 months of treatment with this medicine, and as clinically indicated.

- **if you have diarrhoea and vomiting**. Tell your doctor if you develop any of the following signs and symptoms of stomach or intestinal problems (see section 4 "Possible Side Effects"). Your doctor may provide an antidiarrheal or antiemetic product and/or fluids in order to reduce the symptoms. Your doctor may also withhold temporarily, dose reduce, or discontinue this medicine (see section 3 "How to take this medicine"). You should ask your doctor if use of your treatment for nausea or vomiting medicines together with this medicine may result in a greater risk of heart arrhythmias.

- **if you suffer from bleeding problems.** Tell your doctor if you develop any of the signs and symptoms of blood problems (see section 4 "Possible Side Effects"), because this medicine reduces the capability of your body to stop bleeding. During the first month, your doctor will perform weekly and then monthly complete blood counts for you. Your doctor may also withhold temporarily, dose reduce or discontinue this medicine (see section 3 "How to take this medicine").

- **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 because this medicine reduces the capability of your body to defend from infections.

- **if you have fluid retention**. Tell your doctor if you develop any of the following signs and symptoms of fluid retention during 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). Your doctor will monitor you for fluid retention and will manage your symptoms.

- **if you have heart problems**. Tell your doctor if you have a heart disorder, such as heart failure and decreased blood flow to the heart which can lead to heart attack. Get medical help right away if you get shortness of breath, weight gain, chest pain, or swelling in your hands, ankles or feet.

- **if you have been told you have abnormal heart rhythm**. Tell your doctor if you have 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 this medicine, tell your doctor immediately, as this may be a sign of a serious heart condition (see section 2 "What do you need to know before you take this medicine"). Your doctor will perform an electrocardiogram (ECG) before you start therapy. Your doctor will do a blood test prior to and during therapy and if you have low potassium or magnesium, your doctor will provide a treatment to correct the low blood levels.

- **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. Your doctor will assess how your kidneys are functioning before treatment and will closely monitor how your kidneys are functioning during the course of treatment with this medicine.

- **if you have ever had or might now have a hepatitis B infection**. This is because this medicine could cause hepatitis B to become active again, which can be fatal in some cases. Your doctor will test you for this infection before starting treatment. If you have this infection, your doctor will monitor you closely for signs and symptoms of the infection throughout therapy and several months after you have stopped therapy.

- **if you have or have had pancreas problems.** Tell your doctor if you develop abdominal pain or discomfort. If you have abdominal pain and your blood tests show high levels of lipase, an enzyme that helps your body break down fats in food, then your doctor may interrupt your treatment and perform tests to rule out problems with your pancreas.

- **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 develop a severe skin reaction during treatment, your doctor will permanently discontinue treatment.

- **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 this medicine. Your doctor will be aware of this and may ensure you are adequately hydrated and give you other medicines to help prevent it. Your doctor will perform a blood test to check for high uric acid levels and your doctor will provide a treatment to correct the high levels prior to starting therapy.

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).

Patients of Asian origin
If you are of Asian origin, you may have an increased risk of side effects with this medicine. Your doctor will closely monitor you for serious side effects especially when increasing the dose.

Children and adolescents
This medicine is not recommended for people whose age is under 6 years. It has not been studied in children below the age of 1 year.

Other medicines and Bosutinib Rowex
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 bosutinib 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 Bosutinib Rowex:
- 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 Bosutinib Rowex:
- 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 Bosutinib Rowex. If you are taking any of them, tell your doctor. Your doctor may change the dose of these medicines, change the dose of Bosutinib Rowex, 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 Bosutinib Rowex. If you are taking any of them, tell your doctor.

Acid reducing agents
Proton pump inhibitors (PPIs) should be taken with caution during your treatment with Bosutinib Rowex as they may reduce the effectiveness of Bosutinib Rowex. Your doctor may consider short-acting antacids as an alternative to PPIs and administration times of Bosutinib Rowex and antacids should be separated (i.e. take Bosutinib Rowex in the morning and antacids in the evening) whenever possible.

The medicines listed here may not be the only ones that could interact with Bosutinib Rowex, if you are not sure if the above applies to you or your child, ask your doctor.

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

Pregnancy, breast-feeding and fertility
Bosutinib Rowex is not to be used during pregnancy, unless clearly necessary, because it could harm an unborn baby. Ask your doctor for advice before taking this medicine if you are pregnant or might become pregnant.

Women taking this medicine 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 this medicine 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 this medicine 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 Bosutinib Rowex

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

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

Dose and method of administration
Adults
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 you are not able to tolerate the recommended dose or are not responding to this medicine correctly, your doctor may adjust your dose further.

Children and adolescents (6 years of age and older)
The recommended dose is 300 mg/m^2 body surface area once daily for newly-diagnosed paediatric patients. The recommended dose is 400 mg/m^2 body surface area once daily for resistant or intolerant paediatric patients.
Dose recommendations are provided in the following table. As appropriate, for the recommended dose you may combine different strengths of bosutinib film-coated tablets.

Dosing of bosutinib for newly-diagnosed (ND) and for resistant or intolerant (R/I) paediatric patients

Body surface area	ND recommended dose	R/I recommended dose
0.55–<0.63 m^2	200 mg	250 mg
0.63–<0.75 m^2	200 mg	300 mg
0.75–<0.9 m^2	250 mg	350 mg
0.9–<1.1 m^2	300 mg	400 mg
≥ 1.1 m^2	400 mg*	500 mg*

* maximum starting dose (corresponding to maximum starting dose in adult indication)

In the event you are not able to tolerate the recommended dose or are not responding to this medicine correctly, your doctor may adjust your dose further.
Take the tablets(s) once a day with food. Swallow the tablet(s) whole with water.

If you take more Bosutinib Rowex than you should
If you accidentally take too many 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 Bosutinib Rowex
If a 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 Bosutinib Rowex
Do not stop taking this medicine, 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.

Serious side effects
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 Bosutinib Rowex"):

Very Common (may affect more than 1 in 10 people):
- reduction in the number of platelets (thrombocytopenia), red blood cells (anaemia) and/or neutrophils (type of white blood cells) (neutropenia) which may cause you to have abnormal bleeding, fever, or easy bruising without having an injury (you might have blood or lymphatic system disorder) see section 2 "What you need to know before you take this medicine")
- fluid around the lungs (pleural effusion).

Common (may affect up to 1 in 10 people):
- low white blood cells count (leukopenia)
- bleeding from the stomach or intestine (gastrointestinal haemorrhage) which may include blood in your vomit, stools (bowel movements) or urine, or have black stools (tarry black bowel movements) (see section 2 "What you need to know before you take this medicine")
- chest pain
- toxic damage to the liver (hepatotoxicity), abnormal hepatic function including liver disorder (hepatic function abnormal) which may be accompanied with itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area or fever (see section 2 "What you need to know before you take this medicine")
- when the heart does not pump blood as well as it should (heart failure)
- when there is decreased blood flow to the heart (cardiac ischaemia)
- infection of the lung (pneumonia)
- defect in cardiac rhythm (electrocardiogram QT prolonged) that predisposes to fainting, dizziness and palpitation
- increase in blood pressure (hypertension)
- high level of potassium in the blood (hyperkalaemia)
- acute kidney failure, kidney failure (renal failure), kidney impairment (renal impairment)
- fluid around the heart (pericardial effusion)
- allergic reaction (drug hypersensitivity)
- abnormally high blood pressure in the arteries of the lungs (pulmonary hypertension)
- acute inflammation of the pancreas (pancreatitis acute).

Uncommon (may affect up to 1 in 100 people):
- fever associated with low white blood cell count (febrile neutropenia)
- damage to the liver (liver injury)
- life-threatening allergic reaction (anaphylactic shock)

- abnormal build-up of fluid in the lungs (acute pulmonary oedema)
- skin eruption (drug eruption)
- scaly, peeling rash (exfoliative rash)
- inflammation of the sac-like covering of the heart (pericarditis)
- a marked decrease in the number of granulocytes (a type of white blood cells, granulocytopenia)
- severe skin disorder (erythema multiforme)
- nausea, shortness of breath, irregular heartbeat, muscular cramps, seizure, clouding of urine and tiredness associated with abnormal laboratory 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 (tumour lysis syndrome (TLS))
- respiratory failure.

Not known (frequency cannot be estimated from the available data):
- severe skin disorder (Stevens-Johnson syndrome, toxic epidermal necrolysis) that may include painful red or purplish rash that spreads and blisters and/or other lesions that begin to appear in the mucous membrane (e.g. mouth and lips) due to an allergic reaction
- interstitial lung disease (disorders causing scarring in the lungs): signs include cough, difficulty breathing, painful breathing
- recurrence (reactivation) of hepatitis B infection when you have had hepatitis B in the past (a liver infection).

Other side effects with this medicine may include:

Very common (may affect more than 1 in 10 people):
- diarrhoea, vomiting, stomach pain (abdominal pain), nausea
- fever (pyrexia), swelling of hands, feet or face (oedema), fatigue, weakness
- respiratory tract infection
- nasopharyngitis
- changes in blood test to determine if this medicine is affecting your liver (alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased) and/or pancreas (lipase increased), kidneys (blood creatinine increased)
- decrease of appetite
- joint pain (arthralgia), back pain
- headache
- skin rash, which may be itchy and/or generalised (rash)
- cough
- shortness of breath (dyspnoea)
- feeling of instability (dizziness).

Common (may affect up to 1 in 10 people):
- stomach irritation (gastritis)
- pain
- influenza, bronchitis
- changes in blood test to determine if this medicine is affecting your heart (blood creatine phosphokinase increased), liver (blood bilirubin increased, gamma-glutamyltransferase (GGT) increased), and/or pancreas (amylase increased)

- low level of phosphorus in the blood (hypophosphataemia), excessive loss of body fluid (dehydration)
- pain in the muscles (myalgia)
- alteration of the sense of taste (dysgeusia)
- ringing in the ears (tinnitus)
- hives (urticaria), acne
- sensitivity to UV rays from the sun and other light sources (photosensitivity reaction).
- itching (pruritus).

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: HPRA Pharmacovigilance; website: www.hpra.ie. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Bosutinib Rowex

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 blister 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. Contents of the pack and other information

What Bosutinib Rowex contains
- The active substance is bosutinib. The film-coated tablets come in different strengths.
  Bosutinib Rowex 100 mg film-coated tablets contain 100 mg bosutinib (as dihydrate).
  Bosutinib Rowex 400 mg film-coated tablets contain 400 mg bosutinib (as dihydrate).
  Bosutinib Rowex 500 mg film-coated tablets contain 500 mg bosutinib (as dihydrate).
- The other ingredients are: Microcrystalline cellulose, crospovidone, poloxamer, povidone, magnesium stearate. The film-coating contains hypromellose, titanium dioxide, macrogol, iron oxide yellow (for 100 mg and 400 mg tablets), iron oxide red (for 400 mg and 500 mg tablets) and talc (for 500 mg tablet).

What Bosutinib Rowex looks like and contents of the pack
Bosutinib Rowex 100 mg film-coated tablets are yellow, oval, approximate size 5.41 mm of width and 10.61 mm of length, biconvex, debossed with "100" on one side and "B" on other side.
Bosutinib Rowex 100 mg film-coated tablets are available in blisters in cartons of 28, 30 or 112 film-coated tablets or perforated unit-dose blisters in cartons of 28 x 1, 30 x 1 or 112 x 1 film-coated tablets.

Bosutinib Rowex 400 mg film-coated tablets are orange, oval, approximate size 8.66 mm of width and 16.17 mm of length, biconvex, debossed with "400" on one side and "B" on other side.

Bosutinib Rowex 500 mg film-coated tablets are red, oval, approximate size 9.37 mm of width and 18.20 mm of length, biconvex, debossed with "500" on one side and "B" on other side.

Bosutinib Rowex 400 mg and 500 mg film-coated tablets are available in blisters in cartons of 28 or 30 film-coated tablets or perforated unit-dose blisters in cartons of 28 x 1 or 30 x 1 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Rowex Ltd., Bantry, Co. Cork, Ireland.

Manufacturers
Salutas Pharma GmbH., Otto-von-Guericke-Allee 1, 39179 Barleben, Germany.
Pharmadox Healthcare Limited, Kw20a Kordin Industrial Park, PLA 3000, Paola, Malta.
Lek Pharmaceuticals d.d., Verovškova ulica 57, 1526 Ljubljana, Slovenia.

This medicine is authorised in the Member States of the European Economic Area under the following names:

Austria	Bosutinib Sandoz 100 mg Filmtabletten
	Bosutinib Sandoz 400 mg Filmtabletten
	Bosutinib Sandoz 500 mg Filmtabletten
Belgium	Bosutinib Sandoz 100 mg filmomhulde tabletten
	Bosutinib Sandoz 400 mg filmomhulde tabletten
	Bosutinib Sandoz 500 mg filmomhulde tabletten
Croatia	Bosutinib Sandoz 100 mg filmom obložene tablete
	Bosutinib Sandoz 500 mg filmom obložene tablete
Denmark	Bosutinib Sandoz
France	BOSUTINIB SANDOZ 100 mg, comprimé pelliculé
	BOSUTINIB SANDOZ 400 mg, comprimé pelliculé
	BOSUTINIB SANDOZ 500 mg, comprimé pelliculé
Hungary	Bosutinib Sandoz 100 mg filmtabletta
	Bosutinib Sandoz 400 mg filmtabletta
	Bosutinib Sandoz 500 mg filmtabletta
Ireland	Bosutinib Rowex 100 mg film-coated tablets
	Bosutinib Rowex 400 mg film-coated tablets
	Bosutinib Rowex 500 mg film-coated tablets
Italy	Bosutinib Sandoz
Norway	Bosutinib Sandoz
Poland	Bosutinib Sandoz
Sweden	Bosutinib Sandoz

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