
Chronic Myeloid Leukaemia (CML) - TKIs and TFR

**A Guide for
Patients**

Introduction

This booklet is written for patients with Philadelphia-chromosome-positive (Ph+) CML. This means that you have a genetic abnormality called the Philadelphia Chromosome. If you are unsure if you have this specific subtype of CML, please check with your doctor.

For more information, talk to your haematologist, clinical nurse specialist (CNS) or hospital pharmacist.

This booklet was written and medically reviewed by Fast Facts. We are also grateful to Joanna Burridge, Fran Woodcock, Steven Davies, Colin Heyes and Tracey Littlebury for their contributions as patient reviewers.

If you would like any information on the sources used for this booklet, please email communications@leukaemiacare.org.uk for a list of references.

In this booklet

Introduction	2
In this booklet	3
About Leukaemia Care	4
Tyrosine Kinase Inhibitors and the Philadelphia Chromosome	6
Imatinib	10
Nilotinib	14
Dasatinib	18
Bosutinib	22
Ponatinib: a third-generation TKI	26
Treatment-free remission	31
Future treatments	34
Glossary	36
Useful contacts and further support	39

About Leukaemia Care

Leukaemia Care is a national charity dedicated to ensuring that people affected by blood cancer have access to the right information, advice and support.

Our services

Helpline

Our helpline is available 9.00am - 10.00pm on weekdays and 9.30am - 12.30pm on Saturdays. If you need someone to talk to, call **08088 010 444**

Nurse service

We have two trained nurses on hand to answer your questions and offer advice and support, whether it be through emailing **nurse@leukaemicare.org.uk**, over the phone on **08088 010 444** or via LiveChat.

Patient Information Booklets

We have a number of patient information booklets like this available to anyone who has been affected by a blood cancer. A full list of titles – both disease specific and general information titles – can be

found on our website at **www.leukaemicare.org.uk/support-and-information/help-and-resources/information-booklets/**

Support Groups

Our nationwide support groups are a chance to meet and talk to other people who are going through a similar experience. For more information about a support group local to your area, go to **www.leukaemicare.org.uk/support-and-information/support-for-you/find-a-support-group/**

Buddy Support

We offer one-to-one phone support with volunteers who have had blood cancer themselves or been affected by it in some way. You can speak to someone who knows what you are going through. For more information on how to get a buddy call

08088 010 444 or email
support@leukaemicare.org.uk

Online Forum

Our online forum, **www.healthunlocked.com/leukaemia-care**, is a place for people to ask questions anonymously or to join in the discussion with other people in a similar situation.

Patient and carer conferences

Our nationwide conferences provide an opportunity to ask questions and listen to patient speakers and medical professionals who can provide valuable information and support.

Website

You can access up-to-date information on our website, **www.leukaemicare.org.uk**, as well as speak to one of our care advisers on our online support

service, LiveChat (9am-5pm weekdays).

Campaigning and Advocacy

Leukaemia Care is involved in campaigning for patient well-being, NHS funding and drug and treatment availability. If you would like an update on any of the work we are currently doing or want to know how to get involved, email **advocacy@leukaemicare.org.uk**

Patient magazine

Our quarterly magazine includes inspirational patient and carer stories as well as informative articles by medical professionals. To subscribe go to **www.leukaemicare.org.uk/communication-preferences/**

Tyrosine Kinase Inhibitors and the Philadelphia Chromosome

What is the Philadelphia chromosome?

When you are diagnosed with CML, your white blood cells will be examined under a microscope (known as a cytogenetic test). If the Philadelphia chromosome is identified, the leukaemia is described as Philadelphia-chromosome-positive (or Ph+). Some patients with acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML) also have this Philadelphia chromosome.

In most patients (95%), chronic myeloid leukaemia (CML) is caused by this genetic abnormality in cells in the bone marrow. It arises when a gene called BCR on chromosome 9 fuses with a gene called ABL on chromosome 22, forming the BCR-ABL gene. This makes chromosome 22 smaller than normal - known as the Philadelphia chromosome.

What is the effect of the Philadelphia chromosome?

In Philadelphia-chromosome-positive (Ph+) CML, a new tyrosine kinase is formed that is active all the time, instead of being switched on and off. This causes cells to multiply uncontrollably, producing lots of new immature white blood cells.

In a small number of cases, this affects platelets instead of (or as well as) white blood cells. However, the diagnosis process and the treatment plans that are offered remain the same.

What are tyrosine kinase inhibitors?

Tyrosine kinases are enzymes that can control how white blood cells grow and multiply. The tyrosine kinase inhibitors (known as TKIs for short) have been developed to block the activity of tyrosine kinases. This stops the white blood cells from multiplying and greatly decreases the risk of a

'blast crisis'. This is where 30% or more of white blood cells in the blood and bone marrow are blast cells.

The first TKI – imatinib – was introduced in 2001. Several other TKIs have also been developed since then.

The TKIs have made a big difference to patients with CML and other types of leukaemia. Since the introduction of TKIs, the number of people who survive for 10 years or more with CML has increased to over 80%. The TKIs also cause fewer side effects than traditional chemotherapy used to treat other cancers.

Most people taking TKIs can live a near normal life. However, there can be some impact on your quality of life from time to time through the experience of side effects and other issues. This can be managed through additional treatments and coping strategies.

How do tyrosine kinase inhibitors work?

TKIs are a small molecule that have been engineered to block the BCR-ABL tyrosine kinase and stop it working. This blocks the signals

in the white blood cells that make them grow and multiply, causing them to die.

You will probably have to take TKIs for several years – or even for the rest of your life – to keep the disease under control, but some people are able to take a break when they are responding positively to the treatment. This is called treatment-free remission (see page 31 for more information).

When are tyrosine kinase inhibitors prescribed?

When talking about the treatment of CML, it is important to remember that the disease has three stages, as the treatment depends on the stage of disease:

- **Chronic stable disease** – fewer than 10% of the white blood cells in the blood and bone marrow are blast cells (immature cells that have no function). At this stage, CML is developing only slowly and the patient may have vague symptoms (including tiredness or fatigue, weight loss and maybe even an enlarged spleen) or no symptoms at all.

Tyrosine Kinase Inhibitors and the Philadelphia Chromosome (cont.)

Most patients at diagnosis have chronic stable disease.

- **Accelerated phase** - 10-29% of white blood cells in the blood and bone marrow are blast cells. This leads to more symptoms becoming apparent.
- **Blast phase** - 30% or more of white blood cells in the blood and bone marrow are blast cells and the number of cells is difficult to control. Patients with blast phase (or acute) leukaemia can be very unwell.

The phase of the disease may also change during treatment. Each phase of CML requires different management, but TKIs can be used to treat all phases.



Imatinib

What is imatinib?

Imatinib is one of a group of medicines called tyrosine kinase inhibitors (TKIs). It was the first TKI and is still the most commonly used.

Generic imatinib (see page 13) is now used in the UK but the original brand Glivec is still used in some countries (it is also known as Gleevec).

What is imatinib used for?

- Imatinib is used to treat Ph+ CML in adults and children.
- Imatinib is also used to treat Ph+ ALL in adults and children.
- Imatinib is also a treatment in adults for several different blood disorders, and some rare types of cancer that occur in the stomach or under the skin.

Why is imatinib known as a first-line treatment?

As long as there is nothing to indicate that you will have a

resistance to it, this means that it is the first treatment used after CML has been diagnosed.

How to take imatinib

- Imatinib comes in tablets or capsules, containing either 100mg or 400mg of the medicine.
- Imatinib can be taken once or twice a day, depending on the stage of your CML. Your doctor will tell you how many tablets to take and how often. This will also be shown on the named label on the medicine packaging. It is important that you take the amount you have been told to take. If you are not sure how many tablets to take, contact your doctor or nurse so that they can check your medical notes.
- Swallow the tablets whole with a large glass of water before, during or immediately after a meal (to help avoid stomach upset).
- If you have difficulty swallowing tablets, you can dissolve imatinib tablets in still water

or clear apple juice. Use about 50mL of water or juice for each 100mg tablet. Drop in the tablet and stir with a spoon until the tablet has dissolved completely (the mixture will be cloudy). Drink all the mixture immediately.

- It is a good idea to take the tablet(s) at about the same time every day, to help you remember and to ensure that it is as effective as possible.
- If you forget to take a tablet, take it as soon as you remember, unless it is nearly time to take the next normal dose. In which case, skip the missed tablet. It is important not to take a double dose.
- You should take imatinib every day. It is important to take your medication regularly and as your doctor has prescribed, otherwise the treatment will not have the same effect.
- You can continue taking imatinib until your doctor decides to stop the treatment. This could be because it is

causing unacceptable side effects, or it no longer works effectively.

- If you want to stop taking imatinib for any reason, discuss this with your doctor but continue to take it until you have had this discussion.

Possible side effects of imatinib

You may get some side effects when you first start taking imatinib. They are usually mild to moderate. Some people have very few side effects whereas other people experience more.

Imatinib is still working even if you don't have any side effects.

Most common side effects

Your doctor can prescribe medicines to help with particular side effects if they become troublesome.

- Nausea (feeling sick or queasy), diarrhoea or indigestion
- Headache
- Tiredness (fatigue)

Imatinib (cont.)

- Rash
- Leg aches/cramps or bone pain (during treatment or after you've stopped taking imatinib)
- A build-up of fluid (e.g. puffiness around the eyes or ankles); weight gain

Contact your doctor straight away if you have any of the following side effects as you may need treatment:

- A raised temperature (over 37.5°C [99.5°F] or 38°C [100.4°F], depending on the advice given by your hospital).
- You suddenly feel unwell but your temperature is normal. If you feel shaky or have a sore throat, cough or diarrhoea, or need to pass urine often you may have an infection (imatinib can reduce the number of white blood cells that fight infection).
- Bruising or bleeding that you can't explain (e.g. nose bleed, bleeding gums, blood spots, rashes) – your levels of platelets may be low.
- Rapid weight gain (imatinib can cause your body to retain fluid).

- Eye pain, dry or watery eyes, changes in vision.
- Severe itchy rash.
- Feeling very tired or short of breath – you may have anaemia.

Special considerations:

- Some children and adolescents taking imatinib may have slower than normal growth. For this reason, your doctor will monitor your child's growth at regular intervals.
- Imatinib can make you more sensitive to the sun, so it is important to use sunscreen with a high sun protection factor (such as factor 50) on exposed areas.
- You should not eat grapefruit or drink grapefruit juice when taking imatinib. These slow down removal of imatinib from the body, so levels may build up.
- Imatinib is not recommended during pregnancy. Effective contraceptive should be used during treatment. It is important to be aware that vomiting or diarrhoea may reduce the effectiveness of oral

contraceptives.

- Breast-feeding is not advised during treatment with imatinib.
- Imatinib may make you feel dizzy or drowsy, or can cause blurred vision. Care should therefore be taken when driving, or using tools or machinery.

What happens if imatinib doesn't work for me?

Your doctor will take regular blood tests during treatment to check the number of blood cells (white blood cells, red blood cells and platelets) and to closely monitor how well imatinib is working.

If imatinib doesn't work, or stops working, your doctor will prescribe a different TKI or a different type of treatment.

What is generic imatinib?

All medicines are protected by patent when they first become available, and only the original manufacturer can make the medicine. Once this patent expires, other manufacturers can make copies known as generics.

The manufacturers have to show that their generic version of a medicine works as well as the original and is as safe.

The patent for imatinib expired in December 2016 and other manufacturers are making copies. Patients in England and Wales are now given generic imatinib because it provides better value for money than the original brand (Glivec).

Generic imatinib has exactly the same active ingredient in as Glivec, but may contain different bonding agents.

Nilotinib

What is nilotinib?

Nilotinib is one of a group of medicines called tyrosine kinase inhibitors (TKIs). Its brand name is Tasigna.

What is nilotinib used for?

Nilotinib is used in adults and children for the treatment of Ph+ CML in the chronic phase. It can be used as:

- The first treatment after diagnosis (this is called first-line treatment).
- The second treatment if imatinib doesn't work or causes unacceptable side effects (this is called second-line treatment).

Nilotinib is also used in adults with Ph+ CML in the accelerated phase if imatinib doesn't work or causes unacceptable side effects.

Why is nilotinib known as a second-generation treatment?

The first TKI was imatinib (see page 10). Nilotinib is one of three TKIs that were introduced after imatinib – these are all known as

second-generation TKIs.

The second-generation TKIs work in slightly different ways from imatinib. They are also stronger and may control CML quicker.

Nilotinib may work when imatinib doesn't.

How to take nilotinib

- Nilotinib comes in hard capsules, containing 150mg or 200mg of the medicine.
- Nilotinib is taken twice a day – once in the morning and once in the evening, ideally about 12 hours apart.
- Try to take the medicine at about the same time each day, to help you remember and to ensure that it is as effective as possible.
- Your doctor will tell you how many capsules to take. This will also be shown on the named label on the medicine packaging. It is important that you take the amount you have been told to take. If you are not sure how many capsules to take, contact your doctor or nurse so that they can check

your medical notes.

- Nilotinib capsules must not be taken with food to ensure that the medicine is as effective as possible and absorbed through the body successfully. You should not eat for two hours before taking nilotinib, or for an hour after taking it. This also includes alcohol.
- Swallow the capsules whole with a glass of water.
- If you have difficulty swallowing capsules, carefully cut open the capsule and tip the contents into a teaspoonful of apple sauce or puree and swallow it all straight away. You should not use any more sauce than this, or mix the capsule contents with any other type of food.
- If you forget to take a capsule, wait until the next dose is due. Do not take the missed tablet.
- You should not eat grapefruit or drink grapefruit juice. These slow down removal of nilotinib from the body, so the amount of nilotinib may build up to harmful levels.
- You should take nilotinib every

day. It is important to take your medication regularly and as your doctor has prescribed, otherwise the treatment will not have the same effect.

- You can continue taking nilotinib until your doctor decides to stop the treatment. This could be because it is causing unacceptable side effects, or it no longer works effectively.
- If you want to stop taking nilotinib for any reason, discuss this with your doctor but continue to take it until you have had this discussion.

Possible side effects of nilotinib

You may get some side effects when you first start taking nilotinib. They are usually mild to moderate and should get better after a few days or weeks of treatment. Some people have very few side effects whereas other people experience more.

Nilotinib is still working even if you don't have any side effects.

Nilotinib (cont.)

Most common side effects

Your doctor can prescribe medicines to help with particular side effects if they become troublesome.

- Nausea (feeling sick or queasy)
- Dry or itchy skin, rash
- Headache
- Tiredness/fatigue
- Muscle pain or spasms, pain in joints or bone pain
- Hair loss/thinning

Other common side effects:

- Diarrhoea, vomiting (being sick), wind, or stomach/abdominal discomfort or bloating
- Weight gain
- Loss of appetite or disturbed sense of taste
- Dry or red skin
- Difficulty sleeping
- Changes in mood (e.g. anxiety or depression)

- Feeling dizzy
- Dry, red or itchy eyes
- Rapid heart beat
- Excessive sweating, night sweats or hot flushes

Contact your doctor straight away if you have any of the following side effects as you may need treatment:

- You suddenly feel unwell with or without a high temperature. If you feel shaky or have a sore throat, cough or diarrhoea, or need to pass urine often you may have an infection.
- Bruising or bleeding that you can't explain (e.g. nose bleed, bleeding gums, blood spots, rashes) – your levels of platelets may be low.
- Changes in vision.
- Swelling or pain in one part of the body (you may have a blood clot).
- Itchy rash or painful red lumps.
- Severe abdominal pain.

- Swelling, cough, chest pain, feeling breathless, or suddenly gaining weight – you may have severe fluid retention.
- Excessive thirst, urination or tiredness, or an increase in appetite with weight loss (may be signs of high levels of sugar in the blood).
- Noticeable changes in colour or temperature of toes, fingers, legs or arms (blue, pale or cool could be a sign of a blocked artery).
- Changes to your heart rhythm (e.g. rapid heart rate), chest pain or feeling dizzy – nilotinib occasionally affects the heart.

Special considerations

- Nilotinib is not recommended during pregnancy. Effective contraception should be used during treatment and for up to two weeks after treatment. It is important to be aware that vomiting or diarrhoea may reduce the effectiveness of oral contraceptives.

- Breast-feeding is not advised during treatment with nilotinib.
- Nilotinib may make you feel dizzy or drowsy, or can cause blurred vision. Care should therefore be taken when driving, or using tools or machinery.

What happens if nilotinib doesn't work for me?

Your doctor will take regular blood tests during treatment to check the number of blood cells (white blood cells, red blood cells and platelets) and to closely monitor how well nilotinib is working.

Your doctor will also monitor your pancreas and liver function, the levels of potassium, magnesium, sugar and fats in your blood, and your heart rate.

If nilotinib doesn't work, or stops working, your doctor will prescribe a different TKI or a different type of treatment.

Dasatinib

What is dasatinib?

Dasatinib is one of a group of medicines called tyrosine kinase inhibitors (TKIs). Its brand name is Spyrcelel.

What is dasatinib used for?

Dasatinib is used as:

- The first treatment after diagnosis of Ph+ CML in adults, adolescents and children (at least one year of age) in the chronic phase (this is sometimes called first-line treatment).
- As the second treatment in adults for any phase of CML if previous treatments have not worked or cause unacceptable side effects (this is called second-line treatment).

Dasatinib is also used in adults for the treatment of Ph+ ALL and lymphoid blast CML when earlier treatments haven't worked or cause unacceptable side effects.

Why is dasatinib known as a second-generation treatment?

The first TKI was imatinib. Dasatinib is one of three TKIs that were introduced after imatinib – these are all known as second-generation TKIs.

The second-generation TKIs work in slightly different ways from imatinib. They are stronger and may control CML quicker.

Dasatinib may work when imatinib doesn't.

How to take dasatinib

- Dasatinib comes in tablets containing 20mg, 50mg, 70mg, 80mg, 100mg or 140mg of the medicine. The tablets may be round, oval or triangular, depending on the dose.
- Dasatinib has also been approved in a powder formulation for children and patients who cannot swallow tablets. The dosage prescribed will depend on your child's bodyweight.
- The dose of dasatinib tablets depends on the phase of your

CML. Your doctor will tell you how many tablets to take. This will also be shown on the named label on the medicine packaging. It is important that you take the amount you have been told to take. If you are not sure how many tablets to take, contact your doctor or nurse so that they can check your medical notes.

- Dasatinib is taken once a day.
- Take the tablets at the same time each day to help you remember and to ensure that it is as effective as possible.
- Dasatinib tablets can be taken with or without food.
- Swallow the tablets whole with a glass of water. Do not crush, chew or dissolve the tablets, as they won't work properly.
- If you forget to take a tablet, take the next tablet at the scheduled time. Do not take a double dose.
- You should not eat grapefruit or drink grapefruit juice when taking dasatinib. These slow down removal of dasatinib from

the body, so levels may build up.

- You should take dasatinib every day. It is important to take your medication regularly and as your doctor has prescribed, otherwise the treatment will not have the same effect.
- You can continue taking dasatinib until your doctor decides to stop the treatment. This could be because it is causing unacceptable side effects, or it no longer works effectively.
- If you want to stop taking dasatinib for any reason, discuss this with your doctor but continue to take it until you have had this discussion.

Possible side effects of dasatinib

You may get some side effects when you first start taking dasatinib. Some people have very few side effects whereas other people experience more.

Dasatinib is still working even if you don't have any side effects.

Dasatinib (cont.)

Most common side effects

Your doctor can prescribe medicines to help with particular side effects if they become troublesome.

- Infections (bacterial, viral and fungal)
- Shortness of breath (may be a sign of accumulation of fluid around the heart and lungs)
- Nausea (feeling sick or queasy) or vomiting (being sick)
- Diarrhoea
- Headache
- Tiredness/fatigue
- Pain in the muscles or tummy (abdomen)
- Swelling around the face, hands and feet, which is due to fluid retention
- Dry or itchy skin, or rash
- Bleeding

Contact your doctor straight away if you have any of the following side effects as you may need treatment:

- Chest pain, breathing problems, coughing or fainting – dasatinib occasionally affects the heart.
- You suddenly feel unwell with or without a high temperature. If you feel shaky, have a sore mouth or throat, or have a fever or severe chills, you may have an infection.
- Bruising or bleeding that you can't explain (e.g. nose bleed, bleeding gums, blood spots, rashes) – your levels of platelets may be low.
- Feeling very tired or short of breath – you may have anaemia.
- Blood in your vomit, stools or urine, or if you have black stools.

Special considerations

- Dasatinib is handled by the liver, so certain medicines may stop dasatinib from working properly. Ask your doctor about these.
- Tell your doctor if you are taking medicines to thin the blood or prevent blood clots.
- Dasatinib is not to be used

during pregnancy. Both men and women are advised to use effective contraception during treatment. It is important to be aware that vomiting or diarrhoea may reduce the effectiveness of oral contraceptives.

- Breast-feeding is not advised during treatment with dasatinib.
- Dasatinib may make you feel dizzy or can cause blurred vision. Care should therefore be taken when driving, or using tools or machinery.
- Dasatinib can cause hepatitis B to become active again. Your doctor will check for signs of infection before treatment.

What happens if dasatinib doesn't work for me?

Your doctor will closely monitor how well dasatinib is working by taking regular blood tests.

If dasatinib doesn't work, or stops working, your doctor will prescribe a different TKI or a different type

of treatment.

Bosutinib

What is bosutinib?

Bosutinib is one of a group of medicines called tyrosine kinase inhibitors (TKIs). Its brand name is Bosulif.

What is bosutinib used for?

Bosutinib is used in adults for the treatment of CML. It can be used as:

- The first treatment after diagnosis for Ph+ CML in the chronic phase (this is called first-line treatment) as indicated by the European Medicines Agency (EMA).
- The second treatment for any phase of CML if imatinib, nilotinib or dasatinib don't work or cause unacceptable side effects (this is called second-line treatment).

The use of bosutinib has not been studied in children or adolescents.

Why is bosutinib known as a second-generation treatment?

The first TKI was imatinib. Bosutinib is one of three TKIs that were introduced after imatinib – these are all known as second-generation TKIs.

The second-generation TKIs work in slightly different ways from imatinib. They are stronger and may control CML quicker.

Bosutinib may work when imatinib doesn't.

How to take bosutinib

- Bosutinib comes in tablets containing 100mg, 400mg or 500mg of the medicine.
- Bosutinib is taken once a day, in the morning.
- Take the tablets at about the same time each day to help you remember and to ensure that it is as effective as possible.
- The dose of bosutinib will depend on the phase of your CML, your response to treatment, other medical

conditions and side effects. Your doctor will tell you how many tablets to take. This will also be shown on the named label on the medicine packaging. It is important that you take the amount you have been told to take. If you are not sure how many tablets to take, contact your doctor or nurse so that they can check your medical notes.

- Bosutinib tablets should be taken with food.
- Swallow the tablets whole with a glass of water. Do not crush or dissolve the tablets, as they won't work properly.
- If you forget to take a tablet, take the missed tablet if you remember within 12 hours. If you miss a dose by more than 12 hours take your next tablet at the scheduled time. Do not take a double dose.
- You should not eat grapefruit or drink grapefruit juice, as these may increase the risk of side effects.

- You should take bosutinib every day. It is important to take your medication regularly and as your doctor has prescribed, otherwise the treatment will not have the same effect.
- You can continue taking bosutinib until your doctor decides to stop the treatment. This could be because it is causing unacceptable side effects, or it no longer works effectively.
- If you want to stop taking bosutinib for any reason, discuss this with your doctor but continue to take it until you have had this discussion.

Possible side effects of bosutinib

You may get some side effects when you first start taking bosutinib. Some people have very few side effects whereas other people experience more.

Bosutinib is still working even if you don't have any side effects.

Bosutinib (cont.)

Most common side effects

Your doctor can prescribe medicines to help with particular side effects if they become troublesome.

- Liver or pancreas problems (regular blood tests will show if this is the case)
- Lower blood counts (blood tests may show fewer platelets, red blood cells and/or white blood cells)
- Nausea (feeling sick or queasy) and vomiting
- Less appetite
- Diarrhoea, stomach pain
- Headache
- Tiredness or fatigue, weakness
- Muscle or joint pain
- Fever
- Swelling of the hands, feet or face, nasal passages or back of the throat
- Breathlessness or cough due to fluid around the heart or lungs, or lung infection
- Dry or itchy skin, or rash
- Back pain

Tell your doctor straight away if you have any of the following as you may need treatment:

- You have, or have had, any liver, pancreas or kidney problems. Tell your doctor if you have any discomfort in the stomach area or pain in your side, or if you are passing more or less urine than usual.
- You suddenly feel unwell, with or without a high temperature. If you feel shaky, have a sore throat, cough or diarrhoea, or need to pass urine often you may have an infection.
- An increase in the number of bowel movements per day, or blood in your stools, vomit or urine.
- Bruising or bleeding that you can't explain (e.g. nose bleed, bleeding gums, blood spots, rashes) – your levels of platelets may be low.
- Feeling very tired or short of breath – you may have anaemia.

- Swelling, cough, chest pain, feeling breathless, or suddenly gaining weight – you may have severe fluid retention.
- Changes to your heart rhythm (e.g. rapid heart rate), chest pain or feeling dizzy – bosutinib occasionally affects the heart.

Special considerations

- Some anti-nausea medicines, used in combination with bosutinib, may put you at risk of abnormal heart rhythms.
- Tell your doctor if you are taking any other medicines, as they may not work well with bosutinib.
- Bosutinib is not to be used during pregnancy. Discuss contraception with your doctor. It is important to be aware that vomiting or diarrhoea may reduce the effectiveness of oral contraceptives.
- Breast-feeding is not advised during treatment with bosutinib.
- Bosutinib may make you feel dizzy or can cause blurred

vision. Care should therefore be taken when driving, or using tools or machinery.

- Bosutinib can cause hepatitis B to become active again. Your doctor will check for signs of infection before treatment.

What happens if bosutinib doesn't work for me?

Your doctor will closely monitor how well bosutinib is working by taking regular blood tests.

If bosutinib doesn't work, or stops working, your doctor will prescribe a different TKI or a different type of treatment.

Ponatinib: a third-generation TKI

Most patients with Ph+ CML can be treated successfully with the first- and second-generation TKIs. However, in some patients, treatment with these TKIs can result in drug resistance, i.e. a change in the BCR-ABL gene that prevents the TKIs from working. One of these changes is a mutation known as T315I. You may be tested for this mutation if you show no improvement after taking first- and second-generation TKIs.

To tackle this problem, a third-generation TKI has been produced, called ponatinib, to treat patients with the T315I mutation.

What is ponatinib?

Ponatinib is one of a group of medicines called tyrosine kinase inhibitors (TKIs). Its brand name is Iclusig.

What is ponatinib used for?

Ponatinib is used in adults for the treatment of CML. It can be used for:

- Any phase of CML if nilotinib,

dasatinib or bosutinib don't work or cause unacceptable side effects, and if imatinib is not appropriate.

- Any phase of CML that has the T315I mutation (this is a change in the BCR-ABL gene, which means that the other TKIs do not work – you may be tested for this mutation if there is no improvement after taking other treatments).
- Ponatinib is also used in the treatment of Ph+ ALL.

The use of ponatinib has not been studied in children or adolescents.

Why is ponatinib known as a third-generation treatment?

The first TKI was imatinib. Nilotinib, dasatinib and bosutinib were developed after imatinib and are known as second-generation TKIs. They work in slightly different ways from imatinib. They are stronger and may control CML quicker, and may also work when imatinib doesn't.

Ponatinib was developed after

the second-generation TKIs, so it is known as a third-generation TKI. It works in a slightly different way from the first- and second-generation TKIs.

Ponatinib may work when the first- and second-generation TKIs don't. In particular, ponatinib works when the BCR-ABL gene has the T315I mutation.

How to take ponatinib

- Ponatinib comes in tablets containing 15mg, 30mg or 45mg of the medicine. The different dose tablets are different sizes.
- The dose of ponatinib will depend on the phase of your CML, your response to treatment, other medical conditions and side effects. Your doctor will tell you how many tablets to take. This will also be shown on the named label on the medicine packaging. It is important that you take the amount you have been told to take. If you are not sure how many tablets to take, contact your doctor or nurse so that they can check your medical notes.
- Your doctor will look at your medical history for previous liver, pancreas, kidney, heart or bleeding problems, high blood pressure, alcohol abuse or blood clots. Your doctor will also perform heart and liver function tests before treatment.
- Ponatinib is taken once a day.
- Take the tablets at about the same time each day to help you remember, and to ensure that it is as effective as possible.
- Ponatinib tablets can be taken with or without food.
- Swallow the tablets whole with a glass of water. Do not crush or dissolve the tablets, as they won't work properly.
- If you forget to take a tablet, do not take the missed dose. Take the next dose at the scheduled time.
- You should not eat grapefruit or drink grapefruit juice, as these may increase the risk of side effects.
- You should take ponatinib every day. It is important to take

Ponatinib: a third-generation TKI (cont.)

your medication regularly and as your doctor has prescribed, otherwise the treatment will not have the same effect.

- You can continue taking ponatinib until your doctor decides to stop the treatment. This could be because it is causing unacceptable side effects, or it no longer works effectively.
- If you want to stop taking ponatinib for any reason, discuss this with your doctor but continue to take it until you have had this discussion.

Possible side effects of ponatinib

You may get some side effects when you first start taking ponatinib. Some people have very few side effects whereas other people experience more.

Ponatinib is still working even if you don't have any side effects.

Most common side effects

Your doctor can prescribe medicines to help with particular side effects if they become

troublesome.

- Breathing difficulties, cough
- Nausea (feeling sick or queasy), vomiting, diarrhoea
- Poor appetite
- Liver or pancreas problems (regular blood tests will show if this is the case)
- Infections
- Lower blood counts (blood tests may show fewer platelets, red blood cells and/or white blood cells)
- Problems with heart or blood vessels
- Headache or dizziness
- Tiredness/fatigue
- Muscle pain or spasms, or joint pain
- Swelling in your arms or legs, which is due to fluid retention
- Dry or itchy skin, rash
- Difficulty sleeping

Tell your doctor straight away if you have any of the following as

you may need treatment:

- Breathing difficulties.
- Severe pain in your stomach or back.
- If you suddenly feel unwell, with or without a temperature – for example, if you feel shaky, have a sore throat, cough or diarrhoea, or need to pass urine often – you may have an infection.
- Bruising or bleeding that you can't explain (e.g. nose bleed, bleeding gums, blood spots, rashes) – your levels of platelets may be low.
- Feeling very tired or short of breath – you may have anaemia.
- Swelling, cough, chest pain, feeling breathless, or suddenly gaining weight – you may have severe fluid retention.
- Changes to your heart rhythm (e.g. rapid heart rate), chest pain or feeling dizzy – ponatinib occasionally affects the heart.
- Abnormal pain or sensations in one area of the body – you may

have a blood clot or circulation problems.

Special considerations

- Tell your doctor if you are taking any other medicines, as they may not work well with ponatinib.
- Ponatinib is not to be used during pregnancy. Both men and women are advised to use effective contraception during treatment. It is important to be aware that vomiting or diarrhoea may reduce the effectiveness of oral contraceptives.
- Breast-feeding is not advised during treatment with ponatinib.
- Ponatinib may make you feel dizzy or sleepy, or can cause blurred vision. Care should therefore be taken when driving or using tools or machinery.
- Ponatinib can cause hepatitis B to become active again. Your doctor will check for signs of infection before treatment.

Ponatinib: a third-generation TKI (cont.)

What happens if ponatinib doesn't work for me?

Your doctor will closely monitor how well ponatinib is working by taking regular blood tests.

If ponatinib doesn't work, or stops working, your doctor will prescribe a different TKI or a different type of treatment.

Treatment-free remission

How well do the TKIs work?

The TKIs have provided a huge improvement in the treatment of CML. In 1975, about 1 in 5 patients with CML survived for 5 years. In 2009, two-thirds of patients survived for 5 years. Now, over 80% of patients survive for more than 10 years.

Patients are advised to take TKIs long term, and many patients with CML now have a normal life expectancy when taking TKIs.

Which TKI is right for me?

Your doctor will choose the best TKI for you, depending on your age, overall fitness, other medical conditions and the potential side effects of the different drugs. For example, nilotinib can increase blood sugar levels, so it may not be the right TKI for you if you have diabetes.

When to switch TKI therapy

Your response to TKI treatment will be monitored by regular blood

tests, which include measuring levels of the BCR-ABL gene in the blood. Patients with lower levels of the BCR-ABL gene have a better response to treatment.

For patients on imatinib therapy, if the levels of the BCR-ABL gene are greater than 10% after three months of treatment, you will receive more frequent blood tests between three and six months. If the levels are still above 10% at six months, your doctor may consider switching you to a different TKI.

This approach also applies to patients on second-generation TKIs. Switching therapy has not been shown to have any negative effect on the final outcome, compared to staying on the same treatment.

What is treatment-free remission (TFR)?

It has become clear in clinical trials that treatment with imatinib can achieve what is known as a 'deep molecular response'. This means that the BCR-ABL gene is no longer detected in the blood.

Treatment-free remission (cont.)

About half of all patients who received imatinib as their first treatment for CML in the stable or chronic phase have been able to stop taking imatinib altogether without the CML relapsing (i.e. getting worse again). This is known as treatment-free remission (TFR) because the CML stays in remission without any treatment. In the European STOP TKI study, about half of all patients who stopped taking imatinib had not relapsed after two years.

When is a patient considered to be in treatment-free remission?

Patients who have a deep molecular response are considered to be eligible to attempt TFR and can stop taking the TKI. This means that levels of the BCR-ABL gene in the blood are below a certain level for at least two years whilst taking imatinib.

Patients who stop taking their TKI require close monitoring to ensure their CML is under control.

At the moment, scientists are working out the level of BCR-ABL that can remain in the blood for TFR to be possible, and new tests are being developed. Scientists are also trying to identify factors that might predict who can stop taking TKIs and remain in TFR.

Treatment-free remission is currently only considered for patients who are taking part in clinical trials or involved in a registry, because doctors need to closely monitor what is happening. The data collected in these trials is important to help doctors work out how best to use the TKIs.

What are the risks associated with treatment-free remission?

Stopping TKIs involves weighing up the benefits and risks. Some patients may want to stop treatment with TKIs because they have side effects that affect their quality of life. However, other patients may accept the side effects of continuing with

TKI treatment because this gives them confidence that the CML will not recur.

The key risk of TFR is that CML recurs. For example, in the STOP TKI study, some patients had a relapse of CML more than 30 months after stopping TKIs. So far it appears that a molecular response can be achieved again if the same TKI, or a different TKI, is started again but this is not guaranteed.

Doctors do not yet know what happens if a second TFR is achieved, or if TFR is achieved with a TKI other than imatinib. This will be explored in more clinical trials.

Individual patients need to consider the risks and benefits of stopping or continuing with a TKI and to discuss this with their doctor.

Is treatment-free remission a cure?

A deep molecular response indicates no or very low levels of BCR-ABL, which could be

considered to be a cure. However, there is always the possibility that the disease will recur (relapse), although this becomes less likely the longer the TFR goes on for.

Future treatments

In addition to the T315I mutation, other very rare mutations of the BCR-ABL gene have now been found. None of the TKI therapies work in the patients who have these rare mutations. Researchers are therefore continuing to develop more safe and effective medicines for Ph+ CML.

Asciminib (ABL001) is a new medicine being developed for the treatment of Ph+ CML.

What is asciminib (ABL001)?

Asciminib inhibits the BCR-ABL protein, but in a different way from the TKIs. Instead of blocking the protein, it makes it change shape, disabling it so that it no longer works.

The first-, second- and third-generation TKIs do not work in some patients, or they stop working because of changes (mutations) that develop in the BCR-ABL gene. Because asciminib works in a different way, it is expected to work when the TKIs don't.

Early studies in the laboratory

have shown that asciminib, when used together with nilotinib, got rid of cancer cells in the long term and prevented them from coming back. If this same effect is seen in patients, this combination of medicines has the potential to cure CML completely. This will need to be explored in clinical trials.

Who can have asciminib (ABL001)?

ABL001 is currently being tested in clinical trials involving patients with Ph+ CML who have already had treatment with at least two different TKIs, or in patients with the T315I mutation who have received one TKI therapy.

Asciminib is being tested as a therapy on its own, and in combination with imatinib, nilotinib and dasatinib.

Asciminib is also being tested in patients with Ph+ ALL.

Is asciminib (ABL001) available in the UK?

ABL001 is still in clinical trials. It cannot be prescribed by your

oncologist. However, you may be able to take part in a clinical trial.

So far, clinical trials have produced a recommended dose for asciminib therapy on its own for patients with Ph+ CML who do not have the T315I mutation.

Specific doses are being studied in patients with the T315I mutation.

A study of asciminib–imatinib combination therapy is now planned in patients who have not responded well to initial imatinib therapy.

A study to compare asciminib therapy and bosutinib therapy is also planned.

Glossary

Acute Lymphoblastic Leukaemia (ALL)

Acute lymphoblastic leukaemia (ALL) is a cancer of the white blood cells that would become lymphocytes. Normal white blood cells divide and grow in an orderly and controlled way, however, in leukaemia this process is disrupted. This means signals that stop the body making too many cells are ignored. Cells continue to divide but do not mature into normal lymphocytes (white blood cells).

Acute Myeloid Leukaemia (AML)

Acute myeloid leukaemia (AML) is a type of blood cancer that starts from young white blood cells called granulocytes or monocytes in the bone marrow.

BCR-ABL gene

A fusion gene that is formed when the ABL gene on chromosome 9 and the BCR gene on chromosome 22 swap part of their DNA. The swap-over, or translocation, forms an abnormal fusion gene called BCR-ABL.

Blast cells

Immature cells found in the bone marrow. They are not fully developed and therefore do not carry any particular function within the body. In normal humans, up to 5% of the cells found in the bone marrow are blast cells.

Bone Marrow

The soft blood-forming tissue that fills the cavities of bones and contains fat, immature and mature blood cells, including white blood cells, red blood cells and platelets.

Chemotherapy

A form of cancer treatment that uses one or more anticancer drugs as part of a standardised chemotherapy regime.

Chronic

A human health condition or disease that is persistent or otherwise long-lasting in its effects. The term chronic is usually applied when the course of the disease lasts for more than three months.

Clinical trial

A medical research study involving patients with the aim of improving treatments and their side effects. You will always be informed if your treatment is part of a trial.

Chromosomes

A thread-like structure of nucleic acids and proteins found in the nucleus of most living cells. This carries genetic information in the form of genes.

Chronic Myeloid Leukaemia (CML)

A cancer that affects the blood and bone marrow defined by the presence of BCR-ABL translocation.

Deoxyribonucleic Acid (DNA)

A molecule that carries the genetic instructions used in the growth development, functioning and reproduction of all living organisms.

Fatigue

Extreme tiredness, not alleviated by sleep or rest. Fatigue can be

acute and come on suddenly or chronic and persist.

Generic drug

A pharmaceutical drug that is the equivalent to a brand name product in dosage, strength, route of administration, quality and performance and intended use.

Mutation

The changing of the structure of a gene, resulting in a variant form which may be transmitted to subsequent generations, caused by the alteration of single base units in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes.

Philadelphia Chromosome

The Philadelphia chromosome or Philadelphia translocation is a specific genetic abnormality in which a part of chromosome 22 and chromosome 9 are switched. This is found in leukaemia cancer cells.

Platelets

A disc-shaped element in the blood that assists in blood

Glossary (cont.)

clotting. During normal blood clotting, the platelets clump together (aggregate).

Red Blood Cell

The blood cell that carries oxygen. Red cells contain haemoglobin, which permits them to transport oxygen (and carbon dioxide).

Relapse

The return of a disease or the signs and symptoms of a disease after a period of improvement.

Remission

A period of time when the illness is less severe or is not affecting someone.

Refractory disease

Refractory describes a disease or condition which does not respond to attempted forms of treatment. A cancer is said to be refractory when it does not respond to (or is resistant to) cancer treatment.

Tyrosine Kinase Inhibitor (TKI)

A drug which blocks the action of a tyrosine kinase (a particular type of enzyme in the cell). In CML it works mainly by blocking the activity of the BCR-ABL protein.

White blood cell

One of the cells the body makes to help fight infections. There are several types of white blood cells. The two most common types are the lymphocytes and neutrophils.

Tell us what you think!

If you would like to give us some feedback about this patient information booklet, please hover over the code to the right using your phone or tablet's camera. Click the link as it appears and this will take you to a short web form to fill in.

Suitable for Android, iPhone 7 and above.



Useful contacts and further support

There are a number of helpful sources to support you during your diagnosis, treatment and beyond, including:

- Your haematologist and healthcare team
- Your family and friends
- Your psychologist (ask your haematologist or CNS for a referral)
- Reliable online sources, such as Leukaemia Care
- Charitable organisations

There are a number of organisations, including ourselves, who provide expert advice and information.

Leukaemia Care

We are a charity dedicated to supporting anyone affected by the diagnosis of any blood cancer.

We provide emotional support through a range of support services including a helpline, patient and carer conferences, support group, informative website, one-to-one buddy service and high-quality patient information. We also have a nurse on our help line for any medical queries relating to your diagnosis.

Helpline: **08088 010 444**
www.leukaemiacare.org.uk
support@leukaemiacare.org.uk

Bloodwise

Bloodwise is the leading charity into the research of blood cancers. They offer support to patients, their family and friends through patient services.

020 7504 2200
www.bloodwise.org.uk

Cancer Research UK

Cancer Research UK is a leading charity dedicated to cancer research.

0808 800 4040
www.cancerresearchuk.org

Macmillan

Macmillan provides free practical, medical and financial support for people facing cancer.

0808 808 0000
www.macmillan.org.uk

Maggie's Centres

Maggie's offers free practical, emotional and social support to people with cancer and their families and friends.

0300 123 1801
www.maggiescentres.org

Citizens Advice Bureau (CAB)

Offers advice on benefits and financial assistance.

08444 111 444
www.adviceguide.org.uk

Leukaemia Care is a national charity dedicated to providing information, advice and support to anyone affected by a blood cancer.

Around 34,000 new cases of blood cancer are diagnosed in the UK each year. We are here to support you, whether you're a patient, carer or family member.

Want to talk?

Helpline: **08088 010 444**

(free from landlines and all major mobile networks)

Office Line: **01905 755977**

www.leukaemicare.org.uk

support@leukaemicare.org.uk

Leukaemia Care,
One Birch Court,
Blackpole East,
Worcester,
WR3 8SG

Registered charity
259483 and SC039207

Leukaemia Care
YOUR Blood Cancer Charity

