Answering your questions on
Chronic Myeloid Leukaemia (CML)

glivec
Your guide to understanding CML and Glivec® (imatinib) treatment

The information in this booklet is designed to help you understand chronic myeloid leukaemia (CML) and Glivec, the treatment your doctor has prescribed.

Understanding your disease and its treatment, and knowing what to expect, are important. You are sure to have many questions so, as well as reading this booklet, talk to your doctor about how you feel and any problems you may experience.

Remember:
Medicines only work in people who take them

It is also vital that you continue to take Glivec every day for as long as your doctor prescribes it, even when you feel well. Glivec specifically targets the abnormality that causes CML and, like any medicine, it can only be effective if you continue to take it. Regular appointments with your doctor are important to make sure the treatment is working.

You may also want to contact other people with CML or support groups dedicated to helping people with cancer, and their families. Contact details are provided at the end of this booklet.
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Stem cells (in bone marrow) divide and mature into different types of blood cells:

- **Red blood cells** carry oxygen to other cells in the body.
- **White blood cells** fight infection.
- **Lymphoid stem cells** help blood to clot.
- **Myeloid stem cells** are white blood cells that fight infection.

The stem cells receive signals which turn them on and off as necessary to produce the exact number of blood cells that the body needs.

**Diagnosis of CML**
CML is a rare form of leukaemia. There are around 250 to 300 new cases diagnosed each year in Australia and 50 new cases in New Zealand. The average age of people diagnosed with CML is 50 to 60 years. It affects men and women equally but is very rare in children.

In most cases the cause of CML is unknown, however exposure to high levels of radiation may play a role in a small number of individuals. Like other forms of leukaemia, CML does not run in families.

Often CML is first diagnosed during a routine blood test, before any symptoms occur. Then a bone marrow sample is usually taken, to confirm the diagnosis.

**What is Leukaemia and Chronic Myeloid Leukaemia?**

**Leukaemia** is a type of cancer of the blood and bone marrow - the spongy tissue inside bones, where blood cells develop. As a result of the disease, the body produces too many white blood cells, most of which are abnormal.

Chronic Myeloid Leukaemia (CML) is one type of leukaemia. **Chronic** means it is a slowly growing cancer that may take years to progress. **Myeloid** refers to the type of white blood cells being overproduced.

So **Chronic Myeloid Leukaemia** is a slowly progressing cancer that results in the body producing too many white blood cells of the myeloid type.

**Formation of blood cells**
Bone marrow contains stem cells, which develop into three types of blood cells: red blood cells, white blood cells and platelets.

**Normal blood development**
Stem cells in bone marrow divide and mature into different types of blood cells.

- Red blood cells carry oxygen to other cells in the body.
- Myeloid stem cells are white blood cells that fight infection.
- Lymphoid stem cells help blood to clot.
- Platelets are also white blood cells.

Like other forms of leukaemia, CML does not run in families.
What is Leukaemia and Chronic Myeloid Leukaemia?

How CML develops
People with CML have an abnormal chromosome in their myeloid stem cells and white blood cells. It is called the Philadelphia chromosome, and it is made up of small parts of two normal chromosomes switching places as shown in the diagram below. This abnormal Philadelphia chromosome initially develops in a single myeloid stem cell - the first 'leukaemic cell'. This cell then multiplies to form thousands and eventually millions of daughter leukaemic cells all containing the Philadelphia or Ph chromosome.

Formation of the Philadelphia chromosome
The formation of the Philadelphia chromosome creates a new gene called bcr-abl (pronounced bee-see-are able). This gene controls the production of an abnormal protein called the BCR/ABL protein, which blocks the signals that tell the stem cells to stop producing myeloid white cells. This leads to extremely high levels of myeloid white cells circulating in the blood stream.

CML progresses through three phases: the chronic phase, the accelerated phase and the blast phase.
The three phases of CML

CML progresses through three phases: the chronic phase, the accelerated phase and the blast phase.

<table>
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<tbody>
<tr>
<td>Symptoms</td>
<td>Worsening of symptoms. Fatigue, easy bruising, fever, night sweats, infection, bone pain, abdominal pain and enlarged spleen and liver.</td>
<td>Symptoms get progressively worse. Fatigue, bleeding, fever, weight loss and complications related to infection may occur.</td>
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<tr>
<td>Signs in blood</td>
<td>Increase in number of blast cells in blood and bone marrow. Red blood cells and platelets may decrease.</td>
<td>Further increase in number of blast cells in the blood and bone marrow. Crowding reduces production of normal red blood cells and platelets. Blast cells may spread to other organs</td>
</tr>
<tr>
<td>Length of phase without Glivec*</td>
<td>Often 5 years or more</td>
<td>6–9 months</td>
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* The spleen is an organ on the upper left hand side of the stomach. It removes damaged red blood cells from the circulation and makes some of the white blood cells.

** 'Blast' cells are 'immature' cells that develop into mature white blood cells.

The aim of treatment of CML is to eliminate as many of the leukaemia cells with the Philadelphia chromosome as possible.
How is CML treated?

Stem cell transplantation
(also called bone marrow transplantation)
Stem cell transplantation firstly involves high dose chemotherapy, with or without radiotherapy, which kills all the cells in the bone marrow (normal stem cells as well as leukaemia cells). These cells are then replaced with a transfusion of normal stem cells which may be obtained from the bone marrow or blood stream.

A) Allogeneic stem cell transplantation
This is where stem cells are donated from someone who has stem cells that are considered ‘well matched’ or compatible to the person’s own. This could either be a family member or an unrelated donor.

B) Autologous stem cell transplantation (‘autograft’)
This is where the person’s own stem cells are collected (‘harvested’) when they have shown a good initial response to drug treatment. The stem cells are stored so that they can be re-infused if they are needed later on. This is still a relatively rare procedure and regarded as experimental.

Allogeneic stem cell transplantation from a well-matched donor is the most common type of transplantation used in CML. It is the only treatment that is currently proven to provide a cure for CML in some patients. However, there are risks associated with the procedure, and it is not suitable for everyone, especially older people. The high dose chemotherapy often causes side effects including hair loss and nausea, and can sometimes result in infection and organ failure. A common and often serious complication of allogeneic transplants is ‘graft versus host disease’ in which the donor stem cells react with the person’s own cells, causing damage to liver, skin and other organs.

Interferon alpha
Interferons are natural substances produced by some white blood cells to help fight infection. Although the exact action of interferon alpha is not fully understood in CML, it is given by injection and can slow the growth of leukaemia cells in blood and bone marrow. It has been shown to prolong life in some cases of CML. Interferon alpha is sometimes given alone, and sometimes with the cytotoxic drug cytarabine (ara-C).

Some people cannot tolerate the side effects of interferon therapy, however, better tolerated formulations are being developed.
How is CML treated? continued

Chemotherapy (i.e. hydroxyurea/busulfan)
Chemotherapy is the use of cytotoxic (anti-cancer) drugs to destroy or control the leukaemia cells. Chemotherapies such as hydroxyurea and busulfan are usually used when drugs such as Glivec or interferon are not working as well as expected, or if a person is being prepared for transplantation.

They are used to help reduce the number of myeloid white cells in the blood and to treat some of the symptoms of CML, but have not been shown to prolong life.

Hydroxyurea is also sometimes used while a patient is waiting to begin treatment with Glivec, to help control the number of white blood cells in circulation.

Glivec® (imatinib)
Glivec (also known in the United States as Gleevec®) is a relatively new treatment for CML that specifically targets the genetic abnormality that causes CML.

Comprehensive information on Glivec is provided in the following pages.
All about Glivec

How Glivec works
Glivec targets the cause of CML by blocking the action of the BCR-ABL protein. This protein interferes with the signal to the stem cells in the bone marrow to stop producing myeloid white blood cells.

In this way, Glivec can decrease the number of white blood cells being produced and cause the leukaemia cells with the Philadelphia chromosome to undergo cell death.

Because Glivec acts specifically on the abnormality that causes CML, it is less likely to affect normal cells than other drug therapies used to treat cancer.

What Glivec treatment can achieve
The primary goal of Glivec therapy is to eliminate leukaemia cells with the Philadelphia chromosome.

Glivec has not been proven to ‘cure’ CML, but it has rapidly reduced the disease in many patients with chronic phase CML and has returned some patients with more advanced disease to the chronic phase.

It is important to remember that patients respond differently to therapy. How you respond to Glivec will depend on many factors, but your doctor has prescribed Glivec for you because he or she believes it is the right treatment for you.

To obtain the best chance of a good response to treatment, it is essential that Glivec tablets are taken continuously, exactly as prescribed by your doctor.

Why you must see your doctor regularly
Glivec has not been proven to cure CML. However, if you keep taking it as prescribed, it can usually keep CML under control.

With regular monitoring, your doctor can evaluate how well your blood and bone marrow are responding to Glivec, assess possible side effects and make any necessary adjustments to your treatment. So, even when you are feeling well, it’s important that you keep your regular follow-up medical appointments.

Monitoring your response to treatment
Some tests your doctor may do include:
- A blood test to measure your level of white blood cells, red blood cells and platelets.
- A bone marrow test to measure the number of cells that contain the Philadelphia chromosome.
- A blood or bone marrow test to measure the amount of BCR-ABL present in the body, which indicates the number of leukaemia cells in the body.
- Your doctor may also weigh you on a regular basis and send you for other tests, such as liver function tests, to make sure that your body is not reacting to Glivec in an unexpected way.

Visits to your doctor are also a good opportunity to ask questions and discuss any concerns you may have.

Even when you are feeling well, it’s important that you keep your regular follow-up medical appointments.
Understanding your test results

A Complete Haematological Response (CHR) means that all blood cell types have returned to normal levels. During a haematological response, the leukaemic cells containing the Philadelphia chromosome may still be present.

A Major Cytogenetic Response (MCR) means that the number of leukaemia cells with the Philadelphia chromosome has been considerably reduced i.e. the number of these cells has been reduced from levels as high as 100% at the start of treatment to levels between 1% and 35%.

A Complete Cytogenetic Response (CCR) means that none of the leukaemia cells with the Philadelphia chromosome are able to be detected by standard laboratory methods used to look at chromosomes within cells i.e. Philadelphia chromosome levels of 0%.

A Major Molecular Response (MMR) means that the levels of BCR-ABL have been reduced by at least 1,000 times from an average level seen in patients when they are first diagnosed with CML.

The test that is used to detect the level of BCR-ABL in blood or bone marrow is called Polymerase Chain Reaction (PCR).

PCR-negativity is when the levels of BCR-ABL are reduced to such an extent that they cannot be detected using highly sensitive PCR measurements. This usually reflects a reduction in BCR-ABL of at least 10,000 times from an average level seen in patients when they are first diagnosed with CML.

However, there may still be some leukaemia cells remaining that cannot be detected and it is important to continue taking your Glivec as prescribed by your doctor to help keep the disease under control.

How to take Glivec

Glivec is taken in tablet form, usually once a day. However, your doctor may recommend that you take the tablets in two doses, one in the morning and one in the evening. Taking your Glivec at the same time each day helps you to remember to take it.

Glivec is available as 100mg tablets and 400mg tablets.

Your doctor will have prescribed the appropriate dose for your stage of CML and may change this dose depending on your response to treatment.

How to take your Glivec tablets:
- Usually once a day, at the same time each day
- Never take Glivec on an empty stomach - always take it with a substantial meal and a large glass of water
- Glivec should not be taken with grapefruit juice
- Talk to your doctor before taking any other medicine or supplements
To make sure your Glivec treatment can be effective, you have the important responsibility of taking it every day at the dose your doctor has prescribed.

It is possible that, because of occasional side effects, you will want to take less of your medicine, or not take it at all. However, it is very important for you to continue taking Glivec as instructed, unless your doctor has told you to stop treatment or to reduce the dose.

**Side effects that may occur**

In most people taking Glivec, side effects are mild to moderate. They often occur during the first month or two of treatment and may then decrease after this initial period.

The most common side effects are mild nausea, vomiting, diarrhoea, fatigue, headache, fluid retention, rash, muscle pains and cramps.

Each person's reaction to an anti-cancer drug is different. Some people may have very few side effects, while others may experience more. Tell your doctor about any side effects you have while taking Glivec. In most cases, side effects can be reduced with advice and treatments recommended by your doctor.

Important side effects are discussed in the following section.
Fluid retention
A common side effect with Glivec therapy is fluid retention, also known as oedema. It is most common around the eyes but may also be seen in the ankles or legs.

Occasionally a build up of fluid may occur in other parts of the body, including the lungs, heart and abdomen. Your doctor will monitor you closely and weigh you on a regular basis to prevent complications from occurring.

If you notice any increase in weight or swelling anywhere in your body while taking Glivec, notify your doctor. You may be given a drug called a diuretic which can help reduce the amount of fluids in your body.

Fatigue and anaemia
A feeling of fatigue and tiredness is very common when starting Glivec, and although this generally becomes less noticeable over time, some people do experience it for longer.

It is also common for people to develop anaemia (which means that the blood is less able to carry oxygen to the body, and is sometimes due to low levels of red blood cells or iron). This may add to the feeling of lethargy.

Diarrhoea
If you experience diarrhoea during Glivec therapy, contact your doctor before taking any other drugs. Diarrhoea is usually mild and may be managed with over-the-counter medications.

Nausea and vomiting
Nausea and vomiting is fairly common, especially when first starting Glivec. Heartburn (dyspepsia) may also be experienced quite frequently. Taking Glivec with a substantial meal and a large glass of water may minimise these effects. Splitting higher doses in two (morning and evening) may also help.

Headache
Headaches are a common side effect affecting more than 1 in 10 people taking Glivec. Talk to your doctor if they are severe or become more frequent.

Muscle cramps
Muscle cramps and spasm are usually mild and can generally be managed with electrolyte supplements. If you develop severe muscle cramps while taking Glivec, contact your doctor.

Muscle, bone, and joint pain
Some patients have experienced muscle and bone pains as well as joint pain and swelling while taking Glivec. If you have any pain during treatment, contact your doctor.

Dry skin
Dry, flaky skin has occurred in some patients taking Glivec. This may be helped by using a moisturising cream or bath oil. If this is necessary, ask your pharmacist or doctor for their recommendation.
Glivec and other drugs

Glivec can affect, or be affected by, other medicines or supplements you may be taking. When this happens, Glivec or these other products may lose their effectiveness or produce some unwanted side effects.

Some drugs which may interact with Glivec include warfarin, a medicine to prevent blood clots, certain anticonvulsants to treat epilepsy (such as phenytoin or carbamazepine), medicines for high cholesterol (such as simvastatin), and certain antibiotics (such as erythromycin, roxithromycin, clarithromycin, rifampicin, ketoconazole and itraconazole).

Also included are dexamethasone (a steroid medicine), cyclosporin (a medicine to suppress the immune system), antiviral medicines used treat HIV/AIDS, and some medicines used to treat depression or high blood pressure and heart problems.

It is also recommended that paracetamol (e.g. Panadol®, Panadeine®, Codral®, Tylenol®) is used with caution. In addition, Glivec is known to interact with certain herbal products such as St. John’s Wort [Hypericum perforatum].

Therefore, it is very important to talk to your doctor about medications and supplements you are currently taking, or are planning to take in the future.

Important note: You should avoid eating grapefruit or drinking grapefruit juice while taking Glivec. Grapefruit may increase the levels of Glivec in your blood.

Skin rash

Some patients taking Glivec may develop a skin rash. If you notice any red patches, itchiness, or blistering, contact your doctor. You may be given an additional medication, such as an antihistamine or a topical corticosteroid cream, to reduce the rash.

If additional treatment does not help and the rash becomes severe, your doctor may find it necessary to interrupt your Glivec therapy.

Abdominal pain

It is fairly common for people to develop abdominal pain while taking Glivec. If this is severe, contact your doctor.

Gastrointestinal (GI) bleeding

Although this is relatively rare in people taking Glivec for CML, you should notify your doctor immediately if you observe any blood in your stools or if your stools look very dark in colour.

Other side effects not listed here may happen in some people. Some of these side effects can only be found by laboratory testing and your doctor will be taking blood tests periodically to monitor your status.

If you experience side effects, please consult your doctor. Do not stop taking Glivec or change the dose, unless your doctor tells you to.
Diet and lifestyle
Often simple changes to your diet and lifestyle can help reduce side effects.

- Eat a healthy, balanced diet with fresh fruit and vegetables. Good nutrition will help you cope better with CML and your treatment, and to feel better in yourself.
- To reduce nausea or diarrhoea, always take Glivec with a meal, and avoid foods that you know may upset your stomach such as spicy food.
- If it helps, take your Glivec with your main meal when you feel hungry and eat lighter meals at other times. You may prefer small frequent snacks rather than large meals.
- Eat slowly and chew well to help you digest your food better.
- Drink plenty of water and other fluids each day, to avoid becoming dehydrated.
- Get some light exercise, such as walking.

Getting emotional and practical support

Getting emotional support during your treatment may be just as important as getting medical treatment.

Everyone copes differently with having CML and there is no right or wrong way to react. At times you may feel discouraged, angry, confused or depressed. You may want to get as much information as possible on CML, or you may just need someone to talk to. Your family and loved ones may also have these feelings.

There are a number of organisations and support groups that can help you deal with practical problems relating to transport, employment, social services, etc, as well as providing emotional support.

Contact details are provided at the back of the booklet.
Answers to your questions about Glivec

Q. Will Glivec cure my CML?
A. Glivec has not been proven to ‘cure’ CML. However, if you keep taking it as prescribed, Glivec treatment can reduce the disease in many patients with chronic phase CML and has returned some patients with more advanced disease to the chronic phase.

Q. Can I stop taking Glivec or reduce the dose when I feel well?
A. No. Feeling well means that the Glivec treatment is likely to be keeping your CML under control. If you stop taking Glivec, or reduce the dose, your body may start producing large numbers of white blood cells again and your CML will get worse. Always follow your doctor’s instructions.

Q. Can I reduce the dose of Glivec if I get side effects?
A. You must not reduce your dose of Glivec unless your doctor tells you to. If you have side effects, consult your doctor before making any changes.

Q. Can I take other medicines together with Glivec?
A. Some medicines and Glivec may interfere with each other. These include some medicines you buy without a prescription from the pharmacy, supermarket or health food shop. So you must tell your doctor if you are taking, or want to take, any other medicines, including paracetamol and herbal supplements.
Q. What should I do if I forget a dose of Glivec?
A. Take the missed dose with some food as soon as you remember and then continue taking the tablets at the usual time each day. Don't wait and take a doubledose to make up for the one you missed. If you're not sure what to do, ask your doctor or pharmacist.

Q. Should I take extra Glivec if I have vomiting or diarrhoea?
A. If you vomit or have diarrhoea after taking Glivec, ask your doctor or pharmacist what to do.

Q. Can I drive while I am taking Glivec?
A. Although uncommon, some people get dizziness or blurred vision when they take Glivec, so you should make sure you are not affected in this way, before you drive, operate machinery or do anything that could be dangerous.

Q. Can I drink any alcohol while I am taking Glivec?
A. Check with your doctor before consuming alcohol. Alcoholic beverages may usually be taken with Glivec, but the quantity should be limited to no more than one or two units per day. However, alcohol and Glivec are both processed by the liver. Your doctor may advise you to avoid alcohol if he or she is concerned about your liver health. In addition, if alcohol makes you feel nauseous while taking Glivec, it is best to avoid alcohol.

Q. Can I take Glivec if I am pregnant?
A. No, you should not take Glivec if you are pregnant or planning to become pregnant, because Glivec may be harmful to your unborn baby. You must use contraception if there is a chance of you becoming pregnant, and tell your doctor immediately if you become pregnant while taking Glivec.

If it is necessary for you to take it during pregnancy, your doctor will discuss the risks and benefits involved.

Q. Can I take Glivec if I am breastfeeding?
A. It is not known whether Glivec passes into breast milk, therefore breastfeeding is not recommended.

Q. Where should I store my Glivec?
A. Keep your Glivec in its original container until you take it. Store it in a cool, dry place where it will not get damp or very hot.
Answers to your questions about Glivec

Q. Do I need to protect my skin from the sun?
A. Glivec may cause your skin to be much more sensitive to sunlight than it normally is. Exposure to sunlight can cause skin rash, itching, redness or severe burning. When you are outdoors you should wear protective clothing and use at least a 15+ sunscreen. Do not use a sunlamp.

Q. What if I am unable to swallow tablets?
A. Put the required tablet or tablets in a glass of water or apple juice (approximately 50ml for a 100mg tablet, and 200ml for a 400mg tablet). Stir with a spoon to completely disintegrate the tablet or tablets and immediately drink the whole contents of the glass.
Where to get more information and support

Leukaemia Foundation of Australia
Freecall: 1800 620 420
Email: info@leukaemia.com
Website: www.leukaemia.com

www.novartis.com.au

“Answering your questions on CML” has been prepared by Novartis Oncology, as an aid to patients and their families. It has been reviewed by medical practitioners, patients and health educators.

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