Leukaemia Care
YOUR Blood Cancer Charity

Venetoclax and ibrutinib

This information is about venetoclax and ibrutinib. It is a combination of medicines used to treat some people with chronic lymphocytic leukaemia (CLL). We cover what venetoclax and ibrutinib treatment is, who might have it, and how to take it. We also cover its main side effects and any special precautions you need to take while you're on it.

This leaflet is about venetoclax and ibrutinib used together. We have separate leaflets about ibrutinib and venetoclax used on their own, and venetoclax with other treatments.

This information is aimed at people in the UK. We do our best to make sure it is accurate and up to date, but it should not replace advice or guidance from your health professional.

Summary

- Venetoclax and ibrutinib is a combination of targeted medicines. It is used to treat some people with chronic lymphocytic leukaemia (CLL).
- Ibrutinib and venetoclax both come as film-coated tablets that you take by mouth.
- You take them in cycles. Each cycle is 28 days.
- You usually take ibrutinib on its own for the first 3 cycles, then take venetoclax and ibrutinib for the next 12 cycles.
- The number of tablets you need to take and how often should be printed on the named label on your medicine packaging.
- You will have blood tests to check how well your CLL is responding to treatment.
- Your haematology team will monitor how your body is coping with treatment.
- Some people get side effects. Some people have mild side effects, whereas others get more severe side effects.
- Some side effects can be serious if they are not treated promptly. Contact your haematology team straight away if:
  - You think you might have an infection
  - Your pee is dark or cloudy
  - You have a seizure (fit)
  - You feel weak, exhausted or confused
  - You have pain or bloating in your tummy, diarrhoea or sickness
  - You have difficulty breathing or shortness of breath
  - Your heart rate is fast or uneven, or your pulse is weak or uneven
- Tell your haematology team if you get any other side effects. They may be able to suggest things to help.

This leaflet includes addresses and QR codes that link to webpages for further support. If you cannot access the webpages, please email information@leukaemiacare.org.uk or call **08088 010 444**.

What is venetoclax and ibrutinib?

Venetoclax and ibrutinib is a combination of medicines. It is used to treat some people with chronic lymphocytic leukaemia (CLL).

Ibrutinib is a targeted medicine that blocks a protein called BTK. This protein helps chronic lymphocytic leukaemia cells to grow and multiply. Blocking it stops CLL cells from growing and dividing.

The brand name for ibrutinib is Imbruvica.

Venetoclax is a targeted medicine that helps slow down the progression of CLL. It blocks a protein in CLL cells called BCL-2. This protein stops CLL cells from dying when they should. Blocking it makes the cells self-destruct and die.

The brand name for venetoclax is Venclyxto.

Who might take venetoclax and ibrutinib?

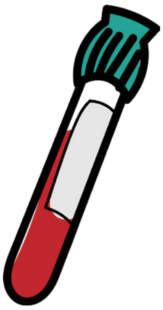
Venetoclax and ibrutinib is suitable for adults. Your haematology team might recommend it if you have CLL that needs treatment and you have not had treatment before.

Treatment aims to reduce your symptoms and keep your CLL under control for as long as possible with as few side effects as possible.

Before taking venetoclax and ibrutinib

Before starting your course of venetoclax and ibrutinib, your haematology team will carry out checks to ensure it is suitable for you. These include:

- Checks of your heart health
- Blood tests to check your blood cell counts
- Blood tests to check your liver and kidney function, and the levels of salts and minerals in your body
- Blood tests to check whether you have any infections that could flare up during treatment, such as viral hepatitis
- A CT scan to find out if CLL is affecting your organs, like your spleen



Your team may recommend other tests, depending on your circumstances.

Your haematology team may ask if there is any possibility you might be pregnant. Neither ibrutinib nor venetoclax should be taken during pregnancy.

Some medicines, supplements and food may interact with venetoclax or ibrutinib. Or they may increase your risk of side effects. It is important to tell your haematology team about any medicines you are taking. This includes prescribed medicines and medicines you have bought yourself without a prescription. Examples include:

- Herbal medicines such as St John's Wort
- Some blood thinners or medicines used to prevent blood clots, like warfarin
- Some medicines to treat infections, including some antibiotics, antifungal and antiviral medicines
- Some medicines used to treat high blood pressure or heart problems
- Some medicines used to prevent or treat stroke, or blood clots in your legs or lungs
- Some medicines used to lower cholesterol
- Some medicines used to treat epilepsy
- Some medicines used to treat depression or obsessive-compulsive disorder
- Some medicines used to treat a rare sleep problem called narcolepsy
- Some cancer medicines
- Some anti-sickness medicines used alongside chemotherapy

Venetoclax and ibrutinib tablets contain several ingredients. Tell your haematology team if you have any allergies or sensitivities.

How do you take venetoclax and ibrutinib?

Venetoclax and ibrutinib both come as tablets you take by mouth.

- Swallow your tablets whole with a glass of water.
- Do not chew, crush, or break your tablets and do not dissolve them in water.
- Try to take your tablets at about the same time each day. Take them with a meal because this helps your body absorb the right amount of venetoclax.
- Avoid grapefruit, bitter oranges (Seville oranges) or starfruit (carambola) while taking venetoclax and ibrutinib. This includes the fruit, fruit juice, or foods or supplements containing them. These foods affect how much medicine your body absorbs.
- Do not take supplements containing St John's Wort while taking venetoclax and ibrutinib. This is because it affects how much medicine your body absorbs.

- You should drink plenty of water to help reduce the side effects of venetoclax. Especially on the days before and the day you start taking it. Also, whenever you increase your dose.
- You need to take medicine to help control your uric acid levels. You usually start this a few days before you begin your course of venetoclax. You carry on taking it until you are on a stable dose of venetoclax, or longer if needed. Your doctor will prescribe this for you.
- You may be given medicine to help prevent shingles or herpes flare-ups.
- If you also take medicines called digoxin or methotrexate, you should take these at least 6 hours before or after taking your ibrutinib.

If you forget to take your tablets

If you forget to take **ibrutinib**:

- Take it as soon as you remember on the same day
- If it's the next day by the time you realise you forgot to take it:
  - Skip the missed dose
  - Take your next dose at the usual time

If you forget to take **venetoclax**:

- Take it as soon as you remember, if it's **within 8 hours** of your dose time.
- If it's **longer than 8 hours** by the time you realise you forgot to take your tablet:
  - Skip the missed tablets
  - Take your next tablets at the usual time the following day
- If you are sick (vomit) after you've taken your tablets, don't take any more tablets that day. Take your next dose at the usual time the following day.

It is important not to take a double dose. If you've taken more venetoclax or ibrutinib than you should, talk to your doctor, nurse or pharmacist. Or go to the hospital immediately. Take your medicine and the leaflet from its box with you.

Dose

Most people on venetoclax and ibrutinib take it in 28-day cycles:

- In the first three cycles, you only take ibrutinib
- For the next 12 cycles, you take venetoclax and ibrutinib

Your haematology team will tell you what dose you'll be on for each 28-day cycle.

Ibrutinib comes as film-coated tablets containing 140mg, 280mg, 420mg or 560mg of ibrutinib. The number of tablets you need to take depends on the dose and strength of the tablets. This should be printed on the medicine packaging. If you are not sure, ask your doctor or nurse.

Most adults with CLL take 420mg of ibrutinib once a day. Your haematology team may suggest a higher or lower dose if needed. They will tell you what dose they recommend for you.

- If you have liver or kidney problems, you usually have a lower dose.
- If you are taking some other medicines, you might also have a lower dose.

Venetoclax comes as film-coated tablets containing 10mg, 50mg or 100mg of venetoclax. The number of tablets you need to take should be printed on the medicine packaging. If you are not sure, ask your doctor or nurse.

You take venetoclax once a day, starting on a low dose of 20mg. Your doctor usually increases the dose over the next 4 weeks until you reach the full dose of 400mg. Your dose is increased slowly to help prevent tumour lysis syndrome (page 14). You might hear people call this the 'ramping up' stage.

Most people increase their dose like this:

- Week 1: Take two 10mg tablets once a day
- Week 2: Take one 50mg tablet once a day
- Week 3: Take one 100mg tablet once a day
- Week 4: Take two 100mg tablets once a day
- Week 5 onwards: Take four 100mg tablets once a day

For the first 4 weeks of treatment with venetoclax, you'll get a new pack each week. They usually come as blister packs with the daily dose you need contained within each blister. This will help you take the right dose each day while your doctor is increasing your dose.

Where do you take venetoclax and ibrutinib?

You take **ibrutinib** at home (or anywhere you are staying). You do not have to go to hospital to have it.

You usually go to a hospital day unit on the day of your first dose of **venetoclax**, and when your dose is increased. This is so you can be monitored closely. Some people may need a short hospital stay.

The rest of the time, you can take venetoclax at home (or wherever you are staying).

You can store both ibrutinib and venetoclax at room temperature. Keep your tablets safe where children cannot see or reach them.

How often do you take it?

You take your tablets once a day, every day. For the first three cycles, you take ibrutinib tablets only with a glass of water. For the rest of your cycles, you take venetoclax and ibrutinib tablets.

- Try to take your tablets at the same time every day, with a glass of water and a meal.
- During the first few weeks of treatment with **venetoclax**, you should take it in the morning, with food. This will help with follow-up blood tests while your doctor increases your dose.

How long do you take it for?

Do not stop taking venetoclax and ibrutinib without discussing it with your haematology team.

You usually have a total of 15 cycles of treatment, where each cycle is 28 days. Once you have completed your treatment, you may go on to active monitoring.

Your haematology team may suggest stopping venetoclax and ibrutinib and trying a different treatment if:

- It is not working well
- It stops working
- You are having side effects that are difficult to cope with
- Check-ups show it is affecting other parts of your body, like your heart, liver or kidneys
- You become pregnant

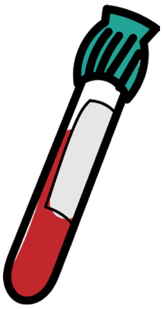
Rarely, stopping ibrutinib may lead to a ruptured spleen. Your haematology team will monitor this by feeling your tummy and doing ultrasound scans.

After stopping ibrutinib, tell your haematology team straight away if you get:

- Pain in the left upper part of your tummy
- Pain below your ribs on the left
- Pain in the tip of your left shoulder

We have more information on active monitoring and treatments for CLL. Follow the link, scan the QR code or search for 'CLL' at www.leukaemiacare.org.uk

How you'll be monitored



Your haematology team will monitor you throughout your treatment. You'll have regular blood tests and other checks when you start taking ibrutinib.

When you first take venetoclax and for each dose increase, you'll have blood tests:

- Before you take your tablets.
- 6 to 8 hours after taking your tablets (or more often, if your team think you need it).
- Around 24 hours after taking your tablets. You usually come back to the hospital for this.

The exact timing of your blood tests may vary. It may depend on where you live and how long it takes you to travel to and from the clinic.

Once you are on a stable dose, your haematology team will continue to monitor you. This is to check how well your treatment is working and how well your body is coping with it.

- You'll have regular blood tests to check:
    - Your blood cell counts
    - How well your liver and kidneys are working
    - The levels of salts, minerals and uric acid in your body
- You'll have regular blood pressure checks
- Your doctor or nurse will examine you to check for heart or lung problems, signs of infection, changes in your skin, or signs of other side effects
- You may have other examinations and scans to check the size of your lymph nodes and organs, like your spleen
- Your team might recommend other tests, depending on your circumstances

What if venetoclax and ibrutinib doesn't work?

If venetoclax and ibrutinib is not working well for you, your doctor will discuss your options with you. They might suggest changing your dose, pausing or stopping treatment. They will talk to you about other treatment options that might be suitable.

Precautions to know about

There are some precautions to be aware of when you are taking venetoclax and ibrutinib.

- Both ibrutinib and venetoclax can make you vulnerable to infections. You might need to take medicines to prevent infections while taking them.
- You should avoid eating grapefruit and starfruit (carambola). This includes the fruit, fruit juice, or foods or supplements containing them.
- You should avoid eating bitter oranges (Seville oranges). This includes the fruit, bitter orange juice or food made with bitter oranges, like marmalade.
- Both ibrutinib and venetoclax may make you feel tired or dizzy, and ibrutinib may also make you feel weak. This might affect your ability to drive or operate machinery.
- Other medicines might interact with venetoclax and ibrutinib and affect how well it works. Your haematology team will tell you whether or how to take other medicines while you're taking it. Or whether you need a different dose of venetoclax and ibrutinib than usual.
- If you need surgery or to have a tooth out, you'll need to stop ibrutinib for a few days before and after. This is to reduce your risk of bleeding. Your doctor will tell you exactly when to stop taking ibrutinib and when to start it again.
- You should not have live vaccines when you have CLL or when you're taking venetoclax and ibrutinib. It is safe to have non-live vaccines. But they might not work as well as they do in other people.

"If you're taking venetoclax and ibrutinib and your GP prescribes you a new medicine, ask them to check that it's safe to take while on your treatment. Your pharmacist can check for interactions with your other medications, too."

Helen, living with CLL since 2015

The Electronic Medicines Compendium has a Venetoclax Patient Alert Card. Follow the link, scan the QR code or search 'venetoclax' at www.medicines.org.uk and click on 'Risk Materials'.

Precautions to prevent tumour lysis syndrome

When you're taking venetoclax, you'll have medicine to help prevent tumour lysis syndrome (page 14). Your dose of venetoclax is also increased very gradually to help prevent it.

You need to drink plenty of water too, as this will also help prevent it. Try to aim for 1.5 to 2 litres of fluid every day. Especially:

- For 2 days before starting venetoclax
- The day you start venetoclax
- Every time you increase your dose

You can include non-alcoholic drinks and non-caffeinated drinks in this amount. But **not** grapefruit, Seville orange or starfruit juice.

If you're struggling to drink enough, your haematology team might give you fluid through a drip before your treatment.

Fertility, pregnancy and breastfeeding info

We do not know what effect venetoclax and ibrutinib has on fertility or pregnancy. Based on animal studies, it may harm unborn babies, especially during the early stages of pregnancy. Venetoclax may also damage sperm.

- If you could get pregnant, it's important to use effective contraception while you are taking ibrutinib or venetoclax and for up to 3 months after you stop.
- We do not know whether venetoclax affects the way hormonal contraceptives work. So, you need to use a barrier method like condoms, a diaphragm or cap when you're on venetoclax and ibrutinib.
- If you're taking ibrutinib or venetoclax and you think you might be pregnant, tell your haematology team as soon as possible.
- If you are planning to get pregnant or to make someone pregnant in the future, tell your haematology team. They will talk to you about your treatment options. They may discuss options to preserve your fertility, such as freezing your eggs or sperm.

Breastfeeding

We do not know if venetoclax or ibrutinib passes into breastmilk or what effect it might have on breastfed babies or children.

You should not breastfeed while you are taking ibrutinib or venetoclax.

Possible side effects

You may get some side effects while you are taking venetoclax and ibrutinib. Some people have very few side effects, whereas others get more serious side effects. They may differ from day to day.

Your haematology team should tell you what side effects to look out for, and who to contact if you need to.

If you are worried about any symptoms or side effects, contact your haematology team. You do not have to wait until your next appointment.

Your haematology team might:

- Prescribe medicines to help manage some side effects
- Suggest things you can do to help you cope with side effects
- Lower your dose of venetoclax and ibrutinib if your side effects are serious or difficult to cope with
- Recommend pausing or stopping venetoclax and ibrutinib, if needed

You can also report side effects via the Yellow Card Scheme. Follow the link, scan the QR code or search for ‘yellow card’ at www.gov.uk. Or search for MHRA Yellow Card in the app store you usually use.

Side effects you might notice

Here, we list some of the more common side effects of venetoclax and ibrutinib. These affect at least 1 in every 100 people who take venetoclax and ibrutinib.

Infections

Contact your team straight away if you think you have an infection. Look out for:

- A high temperature (38°C or higher)
- Shivering, chills or sweating
- Sore throat, sneezing, blocked or runny nose or earache
- Cough, chest pain or shortness of breath
- Burning or stinging when you pee, or peeing more often than usual

Tummy problems

You might get diarrhoea or constipation. You might feel sick or be sick. If you have these side effects, your team can give you medicines to help.

Fatigue

You might experience extreme tiredness or lack of energy.

"Some people have nausea as a side effect and find that taking venetoclax at bedtime helps, after the ramping up stage ends. It reduces side effects, as they sleep through them. Once I was on 400mg a day, with the agreement of my consultant, I changed to taking my tablets at bedtime."

Jane, living with CLL since 2004

Side effects your team might notice

There might be some side effects that your haematology team find during regular checks and blood tests. These include:

- Low levels of white blood cells called neutrophils (neutropenia). This can make you more vulnerable to infection.
- Low levels of red blood cells (anaemia).
- Changes to the level of salts in your blood, which may be a sign of tumour lysis syndrome:
  - High levels of potassium and phosphate
  - Low levels of calcium
  - High levels of uric acid
- Changes in your kidney function.

Rare side effects to know about

Rarely, venetoclax and ibrutinib might cause serious side effects such as tumour lysis syndrome or sepsis. These affect less than 1 in every 100 people taking ibrutinib. So, they do **not** happen to more than 99 in every 100 people. However, if they happen, they can be serious, so it's sensible to know what to look out for.

Tumour lysis syndrome

Venetoclax is very good at killing cancer cells. It can cause many cancer cells to break down all at once. When this happens, the dying cells release a lot of chemicals into your blood. This can cause a serious condition called tumour lysis syndrome.

Tumour lysis syndrome can make you very unwell while your body tries to cope with changes to your body salts and levels of uric acid:

- Your kidneys may work less well
- Your heartbeat may become irregular
- You may have seizures (fits)

It can happen to anyone taking venetoclax to treat CLL. But it's more likely to happen if you have lots of CLL cells in your body. It's also more likely if you have other health problems like kidney disease or a swollen spleen. This is because it's harder for your body to cope with all the chemicals from the dead CLL cells.

Taking ibrutinib before you start venetoclax helps lower your CLL cell number and your chance of tumour lysis syndrome. You are also closely monitored by your haematology team. Most people who get tumour lysis syndrome only have changes on blood tests and do not get symptoms. This is known as ‘chemical tumour lysis syndrome’. However, you still need to know what to look out for, just in case.

Contact your haematology team immediately if you develop any of the following symptoms of tumour lysis syndrome:

- Fever or chills
- Diarrhoea, feeling sick or being sick
- Muscle or joint pain
- Cloudy or dark-coloured pee
- Feeling weak, exhausted or confused
- Irregular heartbeat or shortness of breath
- Pain or bloating in your tummy
- Seizures (fits)

Sepsis

Sepsis is a severe response to an infection. It is a serious condition and needs prompt treatment.

Contact your doctor straight away if you get symptoms of sepsis like:

- Confusion, slurred speech or not making sense
- Blue, grey or pale, blotchy skin, lips or tongue (on black or brown skin look on the palms of the hands or soles of the feet)
- A meningitis-like rash, which does not fade when you roll a glass over it
- Breathing difficulties, such as breathlessness or rapid breathing

"If you have to go to A&E, tell the staff you have blood cancer and the treatment you’re on. Your team might give you a Patient Alert Card to keep with you (page 10). In a medical emergency, these cards let people know what medicine you’re taking and help keep you safe. "

Steve, living with CLL since 2011

Further information

We have more information about CLL including booklets and factsheets to download. Follow the link, scan the QR code or search ‘CLL’ at leukaemiacare.org.uk

We also have booklets you can order in print free of charge. Follow the link or search ‘CLL’ at shop.leukaemiacare.org.uk or scan the QR code.

We’d like to thank the expert reviewers and patient contributors who helped us with this information:

- Dr Dima El-Sharkawi, Consultant Haematologist, The Royal Marsden NHS Foundation Trust
- Helen Knight, CLL Clinical Nurse Specialist, Nottingham University Hospitals
- Patient reviewers and contributors: Helen, Ian, Jane, Steve and Sue

Feedback on this leaflet? Follow the link or scan the QR code to complete a short survey to tell us what we can improve. Or get in touch by email, phone or post.

- Email information@leukaemiacare.org.uk
- Call us on **08088 010 444**
- Write to **Leukaemia Care, One Birch Court, Blackpole East, Worcester, WR3 8SG**

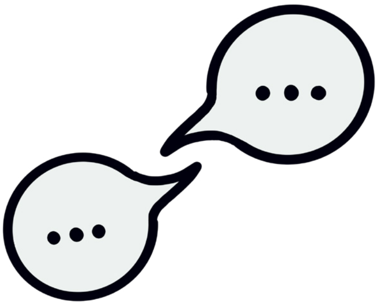
You can also contact us if you’d like a list of the sources we used for this leaflet.

If you need support

We’re here for you if you need support. Follow the link, scan the QR code or search ‘support for you’ at leukaemiacare.org.uk to find out how we can help you.

If you’d like advice, support, or just someone to talk to:

- Call our freephone helpline on **08088 010 444** (weekdays 9am to 4.30pm)
- Send a WhatsApp message to **07500 068065** (weekdays 9am to 5pm)



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Version: 1 Last updated: 08/2025 Review date: 08/2028

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