

Cotellic and Zelboraf Combination Treatment

Patient Booklet



DUAL INHIBITION. REAL IMPACT.

Getting started

About this booklet

The aim of this booklet is to provide answers to questions that are commonly asked by patients who have been prescribed Cotellic (cobimetinib) and Zelboraf (vemurafenib).

This booklet contains useful information to support you throughout your treatment. It is not meant to substitute any guidance, advice or help provided by your healthcare team.

More information on Cotellic and Zelboraf can be obtained from the Consumer Medicine Information (CMI) leaflet that is provided with your medicine or available online at www.medsafe.govt.nz.

If you have any further questions after reading this booklet or the CMIs, or you have any concerns about taking these medications, please contact your healthcare team.

Communication with your healthcare team

In the following pages you will often see the recommendation that you talk with your healthcare team.

This communication is the best way to ensure the most positive experience during your treatment. You should have a good understanding of who your primary contact is, how to reach that person, and when to contact them. Having a clear point of contact and a plan in place makes communication easier if a problem should arise.

You will also learn how to recognise the early signs and symptoms of possible side effects that should be discussed with your healthcare team. Most side effects with this combination are mild, can be managed relatively easily, and do not mean you will need to stop treatment.

As most symptoms have more than one possible cause, you should speak to your healthcare team, who can help uncover the cause and find the most appropriate treatment.

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The glossary

To make this booklet easy to understand, we've included a glossary at the back. This will give you a simple explanation of what each of the terms mean.

Cancer

Cells throughout your body constantly divide to repair damage or replace old cells. This process is finely balanced. Occasionally however, cells grow out of control, forming a tumour.

Some tumours do not invade the surrounding tissue or spread to other parts of the body (metastasise). Doctors call these benign tumours, although in some cases they can cause serious symptoms.

Melanoma is a cancer. This means melanoma can grow into the surrounding tissue. Cancerous cells can also break off from the melanoma and travel to other parts of the body, where they settle. This sows the seeds of another tumour, which grows in another organ. This is called metastatic melanoma.

A biological factory

A cell is, essentially, a biological factory. If you could look inside, you would see pathways connecting various 'machines' and 'areas' in the 'factory'. These pathways switch various areas inside the cell on and off to meet the body's needs.

The various parts of the body communicate, in part, using chemical messengers. Many of these messengers lock onto specific proteins on the outside of cells (called receptors) and can switch the pathways inside a cell on or off. Think of the messenger as your car's ignition key and the receptor as the ignition switch. The key allows you to start or stop your engine. Similarly, the messengers, by binding to their receptor, switch parts of the cell on or off.¹

Reference

1. Ascierto PA, et al. The role of BRAF V600 mutation in melanoma. J Transl Med 2012;10:85

Genes and metastatic melanoma

Your body contains an astonishing amount of DNA.¹ A single strand of your DNA would go from Earth to the Sun and back more than 300 times, or it could be wrapped around the Earth's equator 2.5 million times. DNA is tightly packed into 23 chromosomes that contain the 25,000 or so genes that determine aspects like your natural hair and skin colour, your height and weight, and the pathways inside your cells.

Occasionally, genes give out an incorrect instruction (which is known as a mutation). In many people with metastatic melanoma, these mutations impact certain pathways that are constantly stimulating the cell to divide. The signals that normally switch the pathway off do not work. Imagine a light circuit in your home that has been built with a faulty switch. No matter how many times you click it up and down, the light remains on.

Up to five² in every ten melanomas have a mutation called BRAF^{V600}. This means a pathway that controls cell growth called MAPK² – pronounced 'MAP kin-eyz' (kin as in kind) – becomes stuck 'on'. Combination therapy targets two different steps in the MAPK pathway, blocking the stimulus that encourages the growth of metastatic melanoma. In effect, combination therapy turns off two switches in the circuit.

Healthy cells also use the MAPK pathway. This means that combination therapy can also affect healthy cells, which in turn, may lead to side effects. Your healthcare team has prescribed you a combination therapy which is approved specifically for people with the BRAF^{V600} mutation. It is the best option for your metastatic melanoma at this time.

Reference

1. Annunziato A. DNA packaging: nucleosomes and chromatin. Nature Education 2008; 1: 26. Available at: www.nature.com/scitable/topicpage/dna-packaging-nucleosomes-and-chromatin-310
2. Ascierto PA, et al. The role of BRAF V600 mutation in melanoma. J Transl Med 2012;10:85

Your healthcare contacts

Keep all the information about your contacts here, so you can easily find it, in the one place.

Doctor

Name _____

Phone _____

Email _____

Nurse

Name _____

Phone _____

Email _____

Pharmacy

Name _____

Phone _____

Email _____

Other healthcare providers

Name _____

Service _____

Phone _____

Email _____

Patient support group

Name _____

Phone _____

Email _____

About the treatment

Cotellic in combination with Zelboraf is a targeted treatment for metastatic melanoma.

What is Cotellic?

Cotellic (pronounced ko-tel-ik) is only available in tablet form. The film-coated tablets are white and round with “COB” engraved on one side. You may hear your doctor talk about cobimetinib. This is the “generic” or “non-brand” name for Cotellic. Each Cotellic tablet contains 20 mg of cobimetinib.¹

What is Zelboraf?

Zelboraf (pronounced zel-bohr-af) is only available in tablet form. The film-coated tablets are pinkish white to orange white and oval-shaped with “VEM” engraved on one side. You may hear your doctor talk about (vem-you-raf-e-nib). This is the “generic” or “non-brand” name for Zelboraf. Each Zelboraf tablet contains 240 mg of vemurafenib.²

Cotellic and Zelboraf dual treatment

Targeted therapies, like Cotellic and Zelboraf, attack cancer cells by interfering with their ability to grow, multiply, repair or communicate with other cells. Targeted therapies allow doctors to tailor cancer treatment.

Studies in cancer cells have shown that Cotellic and Zelboraf help reduce overactive signaling by working together. Cotellic + Zelboraf may also affect signaling in healthy cells.^{1,2}

Reference

1. Cotellic CMI, 20 April 2017 2. Zelboraf CMI, 17 March 2017

Settling into a routine

By establishing a routine you can take this combination therapy as your healthcare team has advised and receive its full benefits.

Most people with metastatic melanoma take three tablets of Cotellic once daily for three weeks (then one week break) and four tablets of Zelboraf twice a day every day.

Your doctor may reduce the dose of one or both medicines if you develop side effects that cannot be managed in any other way. However, never stop taking either medicine, or reduce the dose unless your healthcare team advises you to.

You take combination therapy on a cycle that lasts four weeks (28 days):

3x 
once daily

Cotellic dosing¹

You will take three tablets of Cotellic once daily. You take this for **21 consecutive days**: the first three weeks of the four-week cycle.

You then take a week (7 days) off from Cotellic. You still take Zelboraf during your Cotellic-free week.

4x 
every 12 hours

Zelboraf dosing²

You will take four tablets of Zelboraf twice a day, every day. This is a total of eight tablets of Zelboraf a day.

The cycle then begins again

How to take combination therapy

You can take Cotellic with or without food. Take Zelboraf on an empty stomach, at least 1 hour before or at least 2 hours after a meal, in the morning and evening. Do not take an additional dose of either medicine if you vomit after taking your dose. Take your next dose at your regular time.

Swallow both medicines whole with a glass of water. Do not chew or crush the tablets. Do not crush the tablets or mix them with food without speaking to your healthcare team first. Speak to your healthcare team if you have problems swallowing either medicine.

If you forget to take the Cotellic or Zelboraf tablets, take the missed dose as soon as you remember.

- For Cotellic, if it is less than 12 hours before your next dose, skip the missed dose
- For Zelboraf, if it is less than 4 hours before your next dose, skip the missed dose
- Then take the next dose at the usual time
- Do not take a double dose to make up for the dose that you missed
- If you take too much, call your healthcare team, Poison Centre (0800 764 766) or go to your local Accident and Emergency department urgently

Avoid drinking grapefruit juice while you are being treated with Cotellic and Zelboraf.

Tell your healthcare team about any other medicines and supplements you take, including those bought without a prescription or herbal treatments. Similarly, let your pharmacist know and remind your GP that you are taking combination therapy and any other medicine before they suggest a treatment. You could create a list or use a Medication Passport to record medications and other key medical information that you can carry with you.

Seven tips for taking combination therapy

- 1 Make sure you and your carer understand the regimen.** Ask your healthcare team if you are unsure about when and how to take combination therapy
- 2 Keep a checklist of the times you should take combination therapy and the number of tablets.** Cross off each dose after it is taken.
- 3 Try to take combination therapy at the same times each day.** This helps you build a daily routine and acts as a reminder.
- 4 Use an alarm.** Use a watch, phone or timer to remind you when a dose is due.
- 5 Plan.** Your routine may change when you are on holiday, on a day out or away from home. You may need to adjust your timings. Make sure you have sufficient supplies of all your medicines for the time that you are away
- 6 Leave yourself notes** on the refrigerator, next to the TV or on the bathroom mirror reminding you when you need to take your treatment
- 7 Ask for help if you need it.** Ask your partner or carer to remind you to take your dose. Speak to your healthcare team if you have problems opening the packaging, swallowing tablets or remembering to take your medicines. There are often ways around the problem. If you have arthritis or joint pain, a pharmacist can repack the medicines in a container that is easier to open. A pharmacist can also offer aids such as a tablet organiser that allows a week's supply of medicine separated into day and time

Coping with the Side Effects



A delicate balance

Every medicine for every disease can cause side effects, even common medicines such as aspirin, paracetamol and antihistamines. Your healthcare team will help you balance the risks and benefits of a particular treatment. People generally accept more side effects for a potentially life-extending treatment than for a painkiller for a mild headache.

In the next few pages, we will look at some of the most common and important side effects that people taking Cotellic and Zelboraf may experience. Your healthcare team can help you understand the cause and tailor treatment accordingly.^{1,2}

So, watch for possible side effects – without becoming obsessive – and tell your healthcare team about any changes in how you feel. You could use a diary to record the changes. But try not to focus excessively on symptoms. You might find that you start worrying about minor aches and pains that you would previously have dismissed. Focusing excessively on how you feel can exacerbate your pain, discomfort and tension. An early intervention may mean that these side effects do not develop into something that may be more difficult to treat.

If you feel very unwell or are worried, contact your team as soon as you can.

You may not develop the symptoms of some side effects until the adverse event is well established. Your healthcare team may detect changes before problems develop. For example, blood tests can detect the early stage of liver damage. So always make sure that you attend your blood tests and other assessments.

Call your healthcare team as soon as possible if you develop any of the following:

- A rash that covers a large area of your body, blisters, or peeling skin. This rash could occur with fever, chills, aching muscles and generally feeling unwell.
- Symptoms of muscle damage such as:
 - muscle aches
 - muscle spasms and weakness
 - dark, reddish urine
- Symptoms of a serious bleeding problem such as:
 - red or black stools that look like tar
 - blood in your urine or stools
 - unusual vaginal bleeding
 - headaches, dizziness, or feeling weak
- Symptoms of an allergic reaction which may include:
 - shortness of breath
 - wheezing or difficulty breathing
 - swelling of the face, lips, tongue or other parts of the body
 - rash, itching or hives on the skin
- Heart problems, including inadequate pumping of the blood by the heart. Signs and symptoms of a decrease in the amount of blood pumped include:
 - persistent coughing or wheezing
 - shortness of breath
 - tiredness
 - increased heart rate
 - swelling of your ankles and feet
- Any new or worsening problems with your eyes or vision possibly related to a condition called “serous retinopathy” (a build-up of fluid in the eye). These problems may be severe and could lead to blindness.
 - blurred vision, loss of vision or other vision changes
 - changes in colour
 - seeing a blurred outline around objects
 - eye pain, swelling or redness
- severe upper stomach pain, often with nausea and vomiting (signs of inflammation of the pancreas)

The above list includes serious side effects. You may need urgent medical attention.

This is not a complete list of all possible side effects. Other side effects may occur in some people and there may be some others that are not yet known.

Tell your doctor or pharmacist if you notice anything that is making you feel unwell.

Check your skin

People with metastatic melanoma are more likely to develop another skin cancer. So check your skin regularly. Tell your healthcare team as soon as possible if you see any changes such as:

- Rashes, spots, itching, dry or scaly skin
- Hardened or thickened areas of the skin
- Painful red lumps or warts
- Crusty, non-healing sores
- Small lumps that are red, pale or pearly in colour
- New spots, freckles or any moles changing in colour

Ask a friend or family member to check parts of your body that you cannot see yourself.





Rashes

Rashes are among the most common side effects experienced by people taking Cotellic and Zelboraf. Nearly three quarters of people taking combination therapy develop a rash.^{1,2} These are usually mild-moderate but they may emerge at any time during treatment.

If you develop milder reactions call your healthcare team, but do not stop taking combination therapy. Doctors can prescribe antibiotics, steroids or antihistamines (to relieve itch) depending on the type of rash. Applying a thick, alcohol-free emollient cream often soothes dry areas of skin caused by combination therapy.

Combination therapy can cause two types of rash:

Acneiform rash: People develop acne-like papules (red, raised spots) and pustules (spots with pus) on their face, scalp, upper chest and back.

Maculopapular (also called morbilliform) rash: People develop macules (flat, red areas) and papules that resemble measles. Maculopapular rashes usually begin on the upper trunk and then spread to other parts of the body. They can itch intensely.

Each rash is typically associated with either Cotellic or Zelboraf: Cotellic tends to cause acneiform rash, while Zelboraf is associated with maculopapular rash. Rashes can be managed and your healthcare team may reduce the dose of either of the medicines responsible for your type of rash to help manage them.

Reference:

1. Cotellic Data Sheet, 19 June 2017 2. Ascierto Lancet Oncol



Sunburn

About half of people taking Cotellic and Zelboraf develop photosensitivity reactions¹ – in other words, their skin becomes highly sensitive to sunlight.

Photosensitivity is like bad sunburn, with symptoms such as redness, itching, swelling and blistering.

Taking certain precautions means you can usually avoid photosensitivity reactions (see tips on the next page).

People taking combination therapy are especially sensitive to UVA sunlight, which can pass through glass. Occasionally, people taking Cotellic and Zelboraf have reported photosensitivity reactions while indoors or in their vehicle.

Your healthcare team can help distinguish photosensitivity reactions from other skin reactions and may prescribe painkillers, steroids or antihistamines, which can alleviate symptoms.

Reference: 1.Cotellic Data Sheet, 19 June 2017

Safe sun tips



Wear a broad-brimmed hat, sunglasses and clothing with a close weave. Cover as much skin as possible



Avoid direct sunlight as much as possible, especially between 11 am and 3 pm when sunlight is most intense



Use window films that block UVA and UVB in the home, office and vehicle



Apply broad-spectrum sunscreen and lip balm – that protect against UVA, UVB and, if possible, UVC – with a minimum SPF (sun protection factor) of 30 and ideally 50. Cover as much skin as possible, including lips and ears. Reapply every two hours or more frequently after swimming or if you are sweating. Use the sunscreen even on cloudy days and during the winter



Use cosmetics and skin care products that offer as high a SPF as possible. However, this is additional protection: you still need to use sunblock



Hair loss

Typically, hair grows by 12 cm a year and you normally lose about 100 hairs a day. As many cancer treatments target rapidly dividing cells, losing a few more hairs is common. Don't worry if you only see a few hairs on the brush. You need to lose at least half your hair before anyone else will notice.

About 1-in-5 people taking Cotellic and Zelboraf showed some hair loss.¹

Scalp hair is the most susceptible to cancer therapies. Hair loss typically begins 2-3 weeks after treatment starts, usually beginning on the crown and above the ears. You may also lose beard hair, eyebrows, pubic and body hair. Unless you received very high levels of radiotherapy, hair normally grows back within 3-5 months of the end of treatment – although it may be a different texture or colour. Sometimes regrowth begins before treatment ends.

Reference: 1. Ascierto PA, et al. Cobimetinib combined with vemurafenib in advanced BRAF600 mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016; 17:1248-60

What can I do?¹

- If the hair loss causes you distress, speak to your healthcare team, a counsellor or a patient support group
- Some people cut their hair short when they start treatment, which means any loss seems less dramatic. When your hair begins to regrow, you regain your style more quickly
- Hair loss can leave the skin sensitive or tender, even before the loss becomes visible. Some people find warmth, lotions and massage help with sensitivity
- Use mild shampoo, such as a baby shampoo
- Don't wash your hair every day; don't scrub vigorously; pat hair dry
- Use a soft hairbrush
- Avoid using chemicals to curl, straighten or colour hair
- Choose a soft, comfortable covering for the bed pillow
- Think about a wig and hairpiece. A hairdresser can help you style the wig or hairpiece, which you should have fitted properly to stop scalp irritation

When your hair begins to regrow:

- Do not wash your hair more than twice a week
- Massage the scalp to remove dry skin and flakes
- Brush your hair gently and limit pinning, curling, or blow-drying with high heat
- Do not use chemicals to curl or straighten hair until it has regrown. Test any chemical on a small patch of hair first
- Avoid hair colouring for at least three months after treatment

Reference: 1. <http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/vemurafenib/side-effects> Accessed August 2017



Eye Disorders

You should let your healthcare team know urgently if you notice any changes to your sight including:

- Blurred vision, loss of vision or other vision changes
- Changes in colour (yellow tinge to the white part of the eye)
- Seeing a blurred outline around objects
- Eye pain, swelling or redness

Any new or worsening problems with your eyes or vision could be related to a condition called “serous retinopathy” (a build-up of fluid in the eye). These problems may be severe and could lead to blindness.

- Serous retinopathy. The back of your eye is covered with a light-sensitive area called the retina. If you imagine your eye as a camera, the retina is the film or sensor. The retina produces signals that our brains translate into images. The retina consists of 10 layers. In central serous retinopathy, fluid builds up between these layers. This can detach the retina from the back of the eye, impairing sight

Make sure you have your eyes tested regularly and tell your healthcare team if you notice any changes.



Diarrhoea

About 60% of people taking Cotellic and Zelboraf will experience diarrhoea.¹ For most people, this will be mild and easily managed. But for some it might be severe.

Seek help as soon as possible if after a couple of days following your doctor's advice you are passing more than four stools a day. Contact your healthcare team immediately if the diarrhoea is severe, you feel sick or you suffer other symptoms such as stomach pain or cramps, fever or passing dark (tea-coloured) urine.

Your healthcare team can prescribe antidiarrhoeal medicine or suggest those that you can buy from a pharmacist. (Never take any medicine, even bought without a prescription, without speaking to your cancer team first). Don't forget to carry your antidiarrhoeal medicine with you – just in case you need them.

If after a couple of days you still have diarrhoea, seek help from your healthcare team again.

Reference: 1. Ascierto PA, et al. Cobimetinib combined with vemurafenib in advanced BRAF600 mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016; 17:1248-60

Tackling diarrhoea

You can take several dietary steps to build the consistency of your stools, which protects against diarrhoea. In addition, avoid high-fibre, fatty, greasy or spicy foods, which can make diarrhoea worse, and try eating small, frequent meals. Some of these suggestions differ from the usual advice for a healthy diet. If you are unsure, ask your healthcare team to put you in touch with a dietician.

Dehydration

Diarrhoea can mean you lose a lot of fluid. Even mild dehydration can cause, for example: fatigue, poor concentration and memory, headache, and increased tension and anxiety. Drink at least 2.5 litres a day while you have diarrhoea.¹

Try to avoid:

- Coffee, tea, cola, chocolate and other caffeine-containing foods and drink (decaffeinated tea or coffee are fine in small amounts)
- Alcohol
- Carbonated drinks
- Orange and prune juice
- Milk and dairy products (try lactose-free milk or soy milk instead)

You need to pay particular attention to hygiene if you have diarrhoea:

- Use soft wipes to clean yourself after passing stools
- Pat rather than rub yourself
- Use a barrier cream to protect the delicate skin around the anus
- Have plenty of baths or showers, cleaning the area in warm, soapy water

Reference: 1. <http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/vemurafenib/side-effects> Accessed August 2017

Tips with Food

Eat foods that are low in fibre and high in pectin – a water-soluble fibre that seems to counter diarrhoea:



Apples



Apple sauce
(no spices)



Asparagus tips



Avocados



Baked potato
(no skin)



Banana



Beetroot



Plain pasta



White bread



White rice

Eat foods that are high in potassium, an essential mineral lost if you have diarrhoea:

- Asparagus tips
- Avocados
- Banana
- Boiled (no skin) or mashed potatoes
- Fish
- Lactose-free milk



Nausea (feeling sick) and vomiting

About 40%¹ of people taking Cotellic and Zelboraf experience nausea or vomiting. This is usually mild-moderate, but can be severe.

Nausea and vomiting in people with advanced cancer can have many causes including:

- Certain medicines, such as some of those used to treat pain and depression
- Constipation
- Dehydration
- Infections in the mouth and upper airway
- Metastases (spreading cancer), especially in the brain and gut
- Side effects from cancer treatments, including Cotellic and Zelboraf

Tell your healthcare team as soon as possible if you experience nausea or vomiting. Eating well can help you live life to the full despite your metastatic melanoma. Your healthcare team can help uncover the cause and suggest an appropriate treatment, such as:

- Changing medicines, if it causes nausea and vomiting
- Medicines that help control nausea and vomiting

Reference: 1. Cotellic Data Sheet, 19 June 2017



Fatigue (tiredness)

Fatigue can often be a distressing symptom of advanced cancer. Cancer-related fatigue is a profound weariness, weakness and tiredness throughout your body, which often interferes with your ability to perform normal activities.

Numerous factors can trigger or exacerbate fatigue, including treatment with Cotellic and Zelboraf.

Sleep and rest often do not relieve fatigue.

Signs of fatigue

- Feeling weary or exhausted (mentally, physically or emotionally)
- Your body feels heavy, especially your arms and legs
- Less desire to perform everyday activities, such as eating, housework or shopping
- Problems concentrating and thinking clearly
- Shortness of breath, depression and mood disturbances, heart palpitations
- General lack of energy

Tips for fatigue



Tell your healthcare team, who can check for anaemia, deficiencies in certain vitamins, other conditions and certain medicines that might contribute to fatigue. They can suggest treatments that might help



Get some exercise. You might feel like taking it easy, but gentle exercise and activities protect against worsening fatigue, improve wellbeing, counter anxiety and help you sleep. Tailor exercise based on how you feel



Watch for signs of fatigue and pace yourself. This conserves your energy for the tasks that matter. Set yourself priorities and do the most important things when you have the energy. Delegate tasks you do not have to do yourself. Rest when you need to, and schedule rest and relaxation into your day



Eat a healthy diet and drink plenty of fluids. Speak to a dietician or your healthcare team about foods and supplements that could boost your energy



Modify your home. Think about changes that could make life easier. Your healthcare team can refer you to an occupational therapist if you have problems with, for example, dressing, housework or cooking



Joint pain (arthralgia)

Arthralgia – marked discomfort or pain in a joint – is one of the most common side effects caused by combination therapy. About one in four people taking combination therapy experience arthralgia¹ which can hinder everyday activities, such as buttoning clothes, tying shoelaces or writing with a pen.

Again, however, several factors can cause discomfort in the joints, including other cancer treatments, arthritis, and infections. So, tell your healthcare team, who can determine the cause and find the appropriate treatment.

Treating arthralgia

Usually, simple painkillers and medicines that reduce inflammation – such as paracetamol and ibuprofen – alleviate joint pain and increase your mobility. You could also try:

- Exercise
- Acupuncture and electroacupuncture, (where the therapist passes an electric current through the needle)
- Hot baths or holding a heating pad or hot water bottle on the painful joint
- Holding an ice pack or a packet of frozen peas or sweet corn on the painful joint
- Relaxation therapies
- An occupational therapist might be able to suggest aids if you find certain tasks difficult

When to contact your healthcare team

Contact your healthcare team if you:

- Tingling, burning feelings, or pain in your hands or feet
- Joint, muscle or back pain that continues to worry you or is not relieved by pain relief
- Unusual weakness

Reference: 1. Ascierto PA, et al. Cobimetinib combined with vemurafenib in advanced BRAF600 mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016; 17:1248-60



Fever (pyrexia)

A high temperature can arise from several causes. Some tumours seem to produce chemicals that cause fever. An infection can cause a fever. You may be more likely to catch an infection if you have had some types of cancer treatment. A wide variety of other diseases and medicines, including combination therapy, can increase body temperature. Fever usually passes as your body adjusts – a bit like resetting the thermostat on your heater. In the meantime, you can make yourself comfortable.

Make yourself comfortable

Usually taking a medicine such as paracetamol, ibuprofen or aspirin can help bring your temperature down and alleviate pain and discomfort. You may need to take the medicine every 4 to 6 hours until your temperature comes back to normal. Ask your healthcare team which medicine is best for you.

You could also try:

- Removing excess clothing and bed linen
- Having tepid baths or showers, or sponge downs
- Drinking lots of cold fluids
- Sucking on ice cubes or ice lollies
- Opening the window or having a fan in the room
- Resting

If you have the chills, change wet bed linen and clothes, and stay away from drafts and open windows. Do not huddle up under a blanket. Your temperature is still raised and you will just make the fever worse or last longer.

Usually, these approaches will help manage the fever until your temperature returns to normal.

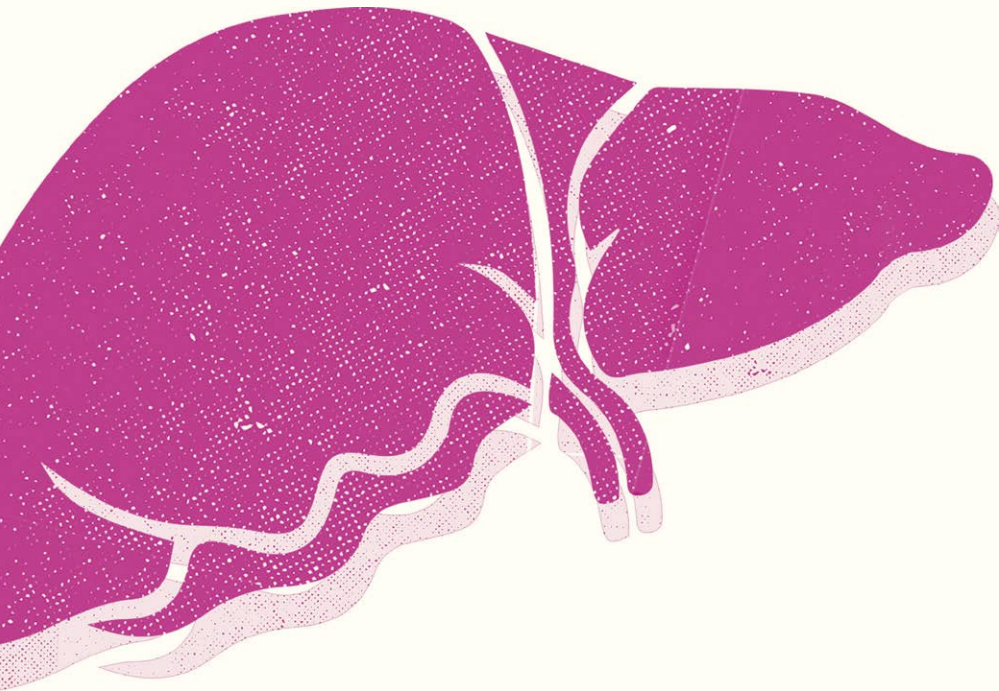
When to seek help

Speak to your healthcare team urgently if:

- You feel very unwell
- You have a rash
- Your temperature doesn't return to normal after a couple of days
- Your temperature remains high: such as over 39.4°C
- You feel faint and lightheaded, which might be a sign your blood pressure is low
- You feel confused or very agitated
- You feel very drowsy

Liver

Your liver is one of the most important parts of your body for keeping it clean and getting rid of waste.



Your liver

Waste removal is probably the liver's best-known role. However, it also has several other critical functions. The liver produces a number of special molecules, called enzymes, which break down potentially hazardous chemicals.

Secondary cancers and some treatments for cancer and other conditions can damage the liver. Liver damage can lead to certain enzymes leaking into your bloodstream.

Blood tests

Your healthcare team will take regular blood samples while you are taking combination therapy to see how well your liver is working. If there is liver damage, levels of enzymes in the blood will be much higher than normal. The healthcare team performs liver function tests to pick up liver damage before symptoms emerge.

Symptoms of liver disease

Tell your healthcare team as soon as possible if you get any of these symptoms, which may indicate that you have a liver problem:

- A yellow tinge to your skin or the white part of your eyes (jaundice)
- Dark or brown (tea colour) urine
- Light coloured stools
- Nausea or vomiting
- Loss of appetite
- Pain on the right side of your stomach
- Bleeding or bruising more easily than usual
- Feeling very tired



Helping yourself

Some people find that complementary medical practices – such as guided imagery, hypnosis, acupuncture and acupressure – relieve nausea and vomiting. These approaches may also help medicines for nausea and vomiting work more effectively.

Other useful tips:

Rinse your mouth out before and after eating

Eat plain, soft, easy-to-digest foods

Eat several small meals a day

Eat dry foods – such as crackers, bread sticks, or toast – throughout the day

Sip fluids throughout the day

Suck on hard sweets – such as peppermints or lemon drops – if your mouth tastes unpleasant

Some people find that spicy foods, fat or greasy foods, and foods that have a strong smell can trigger nausea. Avoid these if they are triggers

Eating cold foods or meals at room temperature often smells less than hot foods

Sit up or lie with your upper body raised for one hour after eating. This helps prevent heartburn and indigestion, which can trigger nausea and vomiting

Try to eat in a well-ventilated room that is not too warm

You might want to avoid your favourite foods when you are feeling nauseous. You might find it triggers nausea and vomiting in the future

A close-up photograph of a person's hands holding a yellow ceramic mug with an orange and green floral pattern. The mug is filled with a brown liquid, likely tea. In the background, an open book is visible, with its pages slightly blurred. The lighting is soft and natural, suggesting an indoor setting with a window.

Adapting your lifestyle

As you continue with your treatment, adapting certain elements of your lifestyle could make everyday life easier.

Some changes you might want to try are:

- Taking more frequent breaks to conserve your energy so that you can still do the things that matter
- Eating smaller, more frequent meals, taking food supplements or eating food that is easier to digest
- Working to try and maintain a consistent sleeping pattern, and finding things to distract you during the day if you feel restless or agitated
- Making some simple adaptations around the home or using aids to make life easier in case your mobility becomes affected. You could ask your healthcare team to refer you to an occupational therapist to help with this
- Monitoring your side effects, as these may change or new ones could emerge if you change treatments.

Ask for help

If you find that you are having difficulty getting on with what you want to achieve, speak to your healthcare team. Do not be afraid to ask for help.

Over time, you may find you need to accept more support and help from professionals, family and friends. Try making a list of things you might need help with, such as housework, gardening or looking after a pet. Do not feel guilty about asking: often family, friends and neighbours want to help, but do not know where to begin or feel uncomfortable raising the subject. Asking for help with specific tasks helps family and friends to help you.

Glossary

Acneiform rash: a type of rash that might develop as a result of taking Cotellic and Zelboraf. People develop acne-like papules (red, raised spots) and pustules (spots with pus) on their face, scalp, upper chest and back.

Arthralgia: joint pain that can be caused by taking Cotellic and Zelboraf that can make everyday activities difficult.

BRAFV600: a specific type of mutation of a protein called BRAF. Zelboraf has been specially designed to target BRAFV600 and interrupt signalling in a specific pathway called MAPK (which stands for mitogen activated protein kinase). By doing this, it can block signals that cause cells to keep growing in a cancer.

Serous retinopathy: a type of eye disorder that can occur in patients taking Cotellic and Zelboraf. Fluid can build up between the layers of the retina (a special light-sensitive layer at the back of the eye), which can cause it to detach and make vision go blurry.

Combination therapy: a term used to describe when two different

therapies are prescribed together. Cotellic + Zelboraf is one such combination therapy.

Cotellic (cobimetinib): a medicine that has been specially designed to target a protein called 'MEK'. MEK is involved in a signalling pathway (called the MAPK pathway) that is involved in cell growth. By targeting MEK, the MAPK pathway is blocked, and cell growth can be reduced.

Maculopapular rash: a type of rash that might develop as a result of taking Cotellic and Zelboraf. People develop macules (flat, red areas) and papules that resemble measles. The rash usually begins on the upper trunk and then spreads to other parts of the body, and can feel very itchy.

MAPK: many cancers are regulated by molecular pathways that send messages from outside a cell, to the machinery inside the cell that makes them grow. The MAPK pathway is an example of such a pathway, and sometimes it can become 'stuck on'. By blocking this pathway, it is possible to reduce the amount of cell growth that takes place.

Melanoma: a type of cancer that develops from melanocytes. It commonly starts in the skin, but can also start in the eye (known as ocular melanoma) or on mucous membranes (known as mucosal melanoma).

Metastasis: the spread of cancer from one site to another not directly connected to it.

Mutation: a permanent change in the DNA sequence that makes a gene.

Photosensitivity: A strong reaction to sunlight, like bad sunburn. People taking Cotellic and Zelboraf should be especially careful in the sun, always wear good quality sunscreen and wear protective clothing. Also see 'Ultraviolet (UV)'.

Pyrexia: increase in body temperature (fever).

SPF: this stands for 'sun protection factor' and describes how much protection a sunscreen will provide from the sun. It is important that people taking Cotellic + Zelboraf always wear a sunscreen with a SPF of at least 30, preferably 50.

Ultraviolet (UV): radiation that is emitted by the sun. It is divided into several subtypes, including UVA and UVB which are responsible for sunburn. UVA sunlight can pass through clouds and glass.

Zelboraf (vemurafenib): a medicine that has been specially designed to target a mutated protein called 'BRAFV600'. BRAFV600 is involved in a signalling pathway (called the MAPK pathway) that is involved in cell growth. By targeting BRAFV600, the MAPK pathway is blocked, and cell growth can be reduced.

Cotellic[®] (cobimetinib), 20 mg film-coated tablets, is a **Prescription Medicine** used in combination with Zelboraf[®] (vemurafenib) to treat a skin cancer called metastatic (spreading) melanoma that has a mutation (abnormal change) in the BRAF gene.

As Cotellic is taken together with Zelboraf, also read the Consumer Medicine Information for Zelboraf before you take these medicines.

Do not use Cotellic if: you are allergic to cobimetinib or any ingredients in Cotellic tablets.

Before taking Cotellic, tell your doctor if: you have any eye problems; you have any heart problems; you have any liver problems; you have any medical conditions that increase your risk of bleeding; you have any muscle problems; you have any problems with your kidneys; you are pregnant or breastfeeding, or plan to become pregnant or breastfeed; you are allergic to any other medicines, foods, dyes or preservatives; you are taking any other medicines, including any that you have bought from a pharmacy, supermarket or health food store.

While you are taking Cotellic: tell your doctor if you notice any skin changes such as crusty, non-healing sores, small lumps that are red, pale or pearly in colour, or new spots, freckles or any moles changing in colour. Avoid going out in the sun. Cotellic can make your skin more sensitive to sunlight. You may burn more easily and get severe sunburn. Avoid grapefruit juice while taking Cotellic. Tell your doctor if you become pregnant while taking Cotellic. Be careful driving or operating machinery until you know how Cotellic affects you, as Cotellic may affect your vision.

Tell your doctor immediately or go to your nearest Accident and Emergency Centre if you notice any of the following: new or worsening problems with your eyes or vision (blurred vision, loss of vision or other vision changes, changes in colour, seeing a blurred outline around objects, eye pain, swelling or redness); a rash that covers a large area of your body, blisters, or peeling skin; symptoms of muscle damage (muscle aches, spasms or weakness, dark, reddish urine); symptoms of a serious bleeding problem (red or black stools that look like tar, blood in your urine or stools, unusual vaginal bleeding, headaches, dizziness, or feeling weak); symptoms of an allergic reaction (shortness of breath, wheezing or difficulty breathing, swelling of the face, lips, tongue or other parts of the body, rash, itching or hives on the skin); symptoms of heart problems (persistent coughing or wheezing, shortness of breath, tiredness, increased heart rate, swelling of your ankles and feet).

Possible common side-effects may also include: diarrhoea, nausea or vomiting; fever or chills; symptoms of dehydration (dry or sticky mouth, low or no urine output, urine looks dark yellow, no tears or sunken eyes); symptoms of anaemia (tiredness, headaches, being short of breath when exercising, dizziness and looking pale); sunburn or sun sensitivity; coughing, difficulty breathing or wheezing; skin problems (rashes, spots, itching, dry or scaly skin, hardened or thickened areas of the skin, painful red lumps or warts). Cotellic has risks and benefits. Ask your doctor if Cotellic is right for you. Use strictly as directed. If symptoms continue or you have side effects, see your healthcare professional. For further information on Cotellic, please talk to your health professional or visit www.medsafe.govt.nz for Cotellic Consumer Medicine Information.

Cotellic is not funded by PHARMAC. You will need to pay for this medicine. A prescription charge and normal doctor fees may apply.

Consumer panel dated 24 May 2017, based on CMI dated 20 April 2017.

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Zelboraf[®] (vemurafenib), 240 mg film-coated tablets, is a **Prescription Medicine** used to treat a skin cancer called metastatic (spreading) melanoma that has a mutation (abnormal change) in the BRAF gene.

Do not use Zelboraf if: you are allergic to vemurafenib or any ingredients in Zelboraf.

Before taking Zelboraf, tell your doctor if: you have a heart disorder or liver or kidney problems; you are pregnant or breast-feeding or plan to become pregnant or breastfeed, you have low levels of potassium, calcium or magnesium in your blood; you have been previously diagnosed with other types of cancer; you are allergic to any other medicines, foods, dyes or preservatives; you are taking any other medicines, including any that you have bought from a pharmacy, supermarket or health food store.

While you are taking Zelboraf, tell your doctor if you notice any skin changes such as a new wart, a sore or reddish bump that bleeds or does not heal. Avoid going out in the sun. Zelboraf can make your skin more sensitive to sunlight. You may burn more easily and get severe sunburn. Tell your doctor if you become pregnant while taking Zelboraf.

Tell your doctor immediately or go to your nearest Accident and Emergency Centre if you notice any of the following: difficulty breathing; chest tightness or wheezing; severe skin rash and/or fever associated with a mild to severe skin rash, severe skin reaction starting with painful red areas, then large blisters and ends with peeling of layers of skin, accompanied by fever and chills, aching muscles and generally feeling unwell; itching or hives, swelling of the face, lips or mouth; severe light-headedness or dizziness, or feel your heart beating irregularly or fast; problems with your eyes or eyesight, such as blurred or altered vision, irritation, eye pain or redness; severe blisters or bleeding of your lips, mouth, nose or eyes; yellowing of the skin and eyes, light coloured bowel motions, dark coloured urine.

Possible common side-effects may also include: rash, itching, dry or scaly skin, skin inflammation (hard, painful red lumps or patches on the skin), other skin problems including warts, sunburn or increased sensitivity to light; loss of appetite and weight loss; headache; changes in the way things taste; tingling, burning or pain in your hands or feet; diarrhoea; constipation; hair loss; joint, muscle or back pain; feeling sick or vomiting; feeling tired; fever; swelling (usually in the legs); cough, frequent infections (fever, chills, sore throat).

Zelboraf has risks and benefits. Ask your doctor if Zelboraf is right for you. Use strictly as directed. If symptoms continue or you have side effects, see your healthcare professional. For further information on Zelboraf, please talk to your health professional or visit www.medsafe.govt.nz for Zelboraf Consumer Medicine Information.

Zelboraf is not funded by PHARMAC. You will need to pay for this medicine. A prescription charge and normal doctor fees may apply.

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