
UNDERSTANDING
PAH

INTRODUCTION

The most important thing to remember when coming to terms with your diagnosis of pulmonary arterial hypertension (PAH) is that you are not alone. Your doctor and healthcare team are there to support you and are the best source of information and reassurance.

Learning you have PAH may be hard to accept. For many people it can cause a variety of feelings, from shock and disbelief, to anger, fear, or sadness. However, other people feel relieved to have a name for their condition and knowing it can be managed with the right treatment. Your focus should be on taking your medicine as your doctor told you and finding the right information. This will help you manage your feelings, manage your well-being, and move forward with your life. This booklet is a good place to start and contains support, guidance, and practical tools to help you.

WHAT IS PAH?

PAH is a rare lung disorder that affects the blood vessels that carry blood from the right side of the heart to the lungs. These blood vessels are called the pulmonary arteries. The movement of blood from the heart to the lungs is an important part of our circulation because blood must have oxygen added to it in the lungs before being pumped around the body. We need this oxygen in our blood to provide enough energy for our bodies to function properly.

As PAH develops, the walls of the pulmonary arteries become thicker, less flexible, and increasingly narrow. This narrowing restricts the blood flow to the lungs and means that the heart finds it harder to pump blood through the arteries, which increases the blood pressure in the pulmonary arteries.

HOW DOES THIS CAUSE THE SYMPTOMS OF PAH?

With the increased blood pressure, the right side of the heart has to work harder still to pump blood through the pulmonary arteries and into the lungs. This causes the right side of the heart to become enlarged. In some cases, over a period of time, the heart can become tired and overworked. Less blood will circulate through the lungs, picking up less oxygen. This can make people feel tired and breathless. If PAH is not treated, the heart can wear out from the effort of trying to pump blood around the body.

HOW COMMON IS PAH?

PAH is a rare condition that can affect women, men, and children of any age or ethnic background. Across the globe, only 10 to 50 people in a million are affected by the condition. This is why not many people have heard about PAH.

DIFFERENT TYPES OF PAH

There are many types of PAH. In some cases, PAH may be associated with other conditions, such as congenital heart disease or connective tissue disease. PAH rarely runs in families. Some of the causes are known and some have yet to be identified. Your doctor can help you understand what type of PAH you have.

CLASSIFYING PAH

Doctors use a detailed system for classifying exactly what type of PAH a person has (see table 1 on the following page). This helps your doctor decide on the best treatment plan. You might also hear the term pulmonary hypertension (PH), which is the overarching classification that PAH sits under.

Table 1. Clinical classification of pulmonary hypertension
Adapted from the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.

1. Pulmonary arterial hypertension
- 1.1. Idiopathic
- 1.2. Heritable
  - 1.2.1. BPMR2 mutation
  - 1.2.2. Other mutations
- 1.3. Drugs and toxins induced
- 1.4. Associated with:
  - 1.4.1. Connective tissue disease
  - 1.4.2. Human immunodeficiency virus (HIV) infection
  - 1.4.3. Portal Hypertension
  - 1.4.4. Congenital heart disease
  - 1.4.5. Schistosomiasis

1.' Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
- 1'.1. Idiopathic
- 1'.2. Heritable
  - 1'.2.1. EIF2AK4 mutation
  - 1'.2.2. Other mutations
- 1'.3. Drugs, toxins and radiation induced
- 1'.4. Associated with:
  - 1'.4.1. Connective tissue disease
  - 1'.4.2. HIV infection

1.'' Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease
- 2.1. Left ventricular systolic dysfunction
- 2.2. Left ventricular diastolic dysfunction
- 2.3. Valvular disease
- 2.4. Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5. Congenital/ acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia
- 3.1. Chronic obstruction pulmonary disease
- 3.2. Interstitial lung disease
- 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4. Sleep-disordered breathing
- 3.5. Alveolar hypoventilation disorders
- 3.6. Chronic exposure to high altitude
- 3.7. Developmental lung diseases

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
- 4.1. Chronic thromboembolic pulmonary hypertension
- 4.2. Other pulmonary artery obstructions
  - 4.2.1. Angiosarcoma
  - 4.2.2. Other intravascular tumours
  - 4.2.3. Arteritis
  - 4.2.4. Congenital pulmonary arteries stenosis
  - 4.2.5. Parasites (hydatidosis)

5. Pulmonary hypertension with unclear and/or multifactorial mechanisms
- 5.1. Haematological disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
- 5.2. Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis neurofibromatosis
- 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
- 5.4. Others: pulmonary tumoral thrombothic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental pulmonary hypertension

HOW DOES PAH AFFECT YOU?

You may have first noticed signs when you are physically active, for instance, climbing stairs, running, walking uphill, or carrying bags. As your PAH develops, you may notice signs more often. You may also find that your symptoms affect the things you can do. PAH is a disease that can get worse over time. Many people find they have good days and bad days.

SOME OF THE COMMON SYMPTOMS OF PAH INCLUDE:

- Shortness of breath, especially with physical activity
- Feeling tired
- Dizziness

OTHER SYMPTOMS THAT YOU MAY ALSO NOTICE INCLUDE:

- Chest discomfort or pain
- A fast and/or irregular heart beat (also called palpitations)
- Light-headedness or fainting
- Swelling in your arms, legs, or ankles (also called fluid retention or oedema)

HOW DO DOCTORS MEASURE THE SEVERITY OF PAH?

You may have heard your doctor refer to Functional Class. This is simply a way for him or her to measure the effect that PAH is having on your day-to-day living. It provides a useful tool when considering your treatment plan. The Functional Class system has 4 levels to describe how severely PAH affects your life. Your PAH doctor will use this system to assess how severe your PAH symptoms are. The table opposite describes the 4 levels.

CLASS	I	II	III	IV
How symptoms affect you	You have no symptoms with normal daily activities	You have some symptoms with normal daily activities AND some limits when doing physical activity	You may feel symptoms when doing less than your normal activity. You may also feel more limits when doing physical activity	You may feel symptoms with any kind of activity, including while resting

YOU ARE STILL YOU

Regardless of the fact that you have just learned you have PAH, or have been living with PAH for a while, you are still the same person. Making adjustments to your everyday life, based on how you are feeling and what you want to do, will help you stay in control of your life.

DIAGNOSIS

Because symptoms of PAH resemble those of other conditions, it is quite difficult to diagnose PAH. There is often a lengthy delay between first visiting the doctor and receiving specialist care at a hospital.

There is no single test that will tell the healthcare team if someone has PAH. It is important for them to consider all diseases that may be associated with PAH, as well as other causes of breathlessness, such as lung and heart diseases and blood clots. The healthcare team will first rule out any other diseases that may be causing the symptoms.

If the healthcare team suspects that someone has PAH they will follow several initial steps to confirm the diagnosis. These tests could reveal the person has a disease other than PAH. Depending on the results of the tests, the healthcare team may then take a different approach towards future investigations.

COMMON TESTS FOR PAH

There are many other tests that the PAH team might perform, depending on each person's individual symptoms.

PERSON WITH PAH SYMPTOMS

CONSIDERATION OF MEDICAL AND FAMILY HISTORY; MEDICATIONS

ECHOCARDIOGRAM (ECHO) CHEST X-RAY
ELECTROCARDIOGRAM (ECG)

WALKING TESTS

RIGHT HEART CATHETERIZATION

DIAGNOSTIC TESTS

There are many different sorts of tests doctors can use to decide if a person has PAH or not. Some of the tests are repeated at different times to assess how well a treatment plan is working or to check the PAH symptoms haven't got any worse. Some of the more common tests are explained below.

ELECTROCARDIOGRAM (ECG)

An ECG examination records the electrical activity of your heart. Small metal contacts called electrodes are stuck to your chest and record the electrical signals that relate to your heart beat. The test only takes a few minutes and is often repeated when someone living with PAH attends a clinic appointment.

ECG testing allows the heartbeat to be analysed and any problems with the heart's rhythm to be picked up.

CHEST X-RAY

Chest X-rays show a good view of the lungs, along with an outline of the shape and size of the heart and the pulmonary arteries. The X-ray can provide clues to non-PAH causes of breathlessness, such as scarring of the lung. It can also reveal certain abnormalities of the heart and lungs that are characteristic of PAH.

Sometimes, people with PAH can have an enlarged heart and doctors may be able to see this on the chest X-ray.

ECHOCARDIOGRAM

The 'echo' or echocardiogram uses ultrasound to display a moving picture of the heart. The test is very safe and is often repeated when someone with PAH has a clinic appointment.

A technician passes a device over your chest area at various angles and can see the heart moving on a connected screen. Echo can be used to look at things like heart abnormalities and the amount of blood being pumped from the heart with each beat. It can also be used to provide a rough estimate of blood pressure in the pulmonary arteries.

LUNG FUNCTION TESTING

Lung function tests provide information about the amount of air a person's lungs can hold and how effectively they work. By comparing the person's results with those of healthy people of the same age and height doctors can tell if the patient's airways are narrower or less effective than normal. Lung function testing can be particularly useful in people living with PAH who also have a lung condition.

WALK TESTS

Walk tests assess how able a person is to exercise. The 6-minute walk test requires you to walk as far as you can up and down a corridor in 6 minutes. The shuttle walk test is similar but requires you to walk up and down a 10-metre distance at increasingly faster speeds until you get too breathless to continue. Your blood pressure, heart rate and oxygen levels will be assessed. You may also be asked to wear a blood pressure monitor.

Walk tests help to identify a person's ability to undertake normal day-to-day activities. They can also be a good way of measuring how effective drug treatments are or if any changes in treatment are needed.

CARDIOPULMONARY EXERCISE TESTING

In cardiopulmonary exercise testing (CPET) you breathe into a mouthpiece while riding an exercise bike or walking on a treadmill. You will also be connected to an ECG machine, to monitor your heart. The results from these tests help to explain how able the lungs, heart and muscles are to use the oxygen you breathe.

VENTILATION-PERFUSION SCANNING

Ventilation-perfusion scanning is a two-part test measuring breathing and blood-flow in the lung and helps tell doctors about the 'evenness' of airflow and blood-flow to the lungs.

The scan results show a low, medium or high probability of blood clots in the lung. One of the more common types of PAH occurs in people who have developed recurrent blood clots in their lungs over a long period of time.

COMPUTERISED TOMOGRAPHY (CT)

CT scanning uses X-rays to show multiple cross-sections (slices) through the chest. CT scanning requires you to lie on a bed that slowly moves forwards and backwards through the scanner. The images give helpful information about the heart and can help identify blood clots.

MAGNETIC RESONANCE IMAGING (MRI)

An MRI scan uses a strong magnetic field and radio waves to create detailed pictures of the heart, lungs and large blood vessels, and surrounding tissues. The MRI scanner is like a tunnel about 1.5 metres long surrounded by a large circular magnet. You lie on a couch, which then slides into the scanner.

MRI can also produce moving pictures of the way the heart is working and help to identify if it is struggling to work normally. MRI scans are very safe and can be repeated without problems.

RIGHT HEART CATHETERISATION (RHC)

RHC allows the healthcare team to obtain a precise measurement of the blood pressure in the heart and pulmonary artery. RHC provides information that will confirm the diagnosis of PAH and confirm or exclude some other causes of PAH.

RHC is usually performed in hospitals. With you lying still, a thin flexible tube called a catheter is inserted through a vein in your groin or neck and slowly fed into the right side of your heart and then your pulmonary artery. The catheter allows doctors to measure blood pressure in several places at once. An estimate of the blood flow through the heart and body is also recorded.

Some of the tests conducted during your diagnosis might be repeated periodically during your regular risk assessments.

Please discuss with your PAH team for more information.

Table 2. Suggested frequency of tests for PAH.
Adapted from the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

	At diagnosis	Every 3–6 months	Every 6–12 months	3–4 months after changes in therapy	If symptoms get worse
Medical assessment and determination of functional class	+	+	+	+	+
ECG	+	+	+	+	+
Walking test	+	+	+	+	+
CPET	+		+	+	+*
Echo	+		+	+	+
Basic blood tests- including NT-proBNP	+	+	+	+	+
Extended blood tests	+		+	+	+
Blood gas analysis	+		+	+	+
RHC	+		+*	+*	+*

*Should be considered

RISK ASSESSMENT

By gathering information provided from a variety of different tests, PAH doctors are able to assign a "risk category" to a person living with PAH. The categories are Low, Intermediate, and High and they indicate what the risk is that the person will die within 1 year.

Table 3 shows what different test results mean.

This might sound scary, but it actually helps doctors make sure a person is on the right treatment plan. The goal of treatment should be to move people in the Intermediate and High risk categories down into the Low risk category. For those people who are already in the Low risk category the goal of treatment is to make sure they stay there. By regularly testing a person with PAH (see Table 2), doctors closely monitor how the person's treatment plan is working and can make adjustments to their medication if necessary.

The goal of treatment is to move people with PAH into the 'Low-risk' category, or help them stay there. Regular testing helps doctors closely monitor how effective treatment plans are, and make any necessary changes.

Table 3. Assessing risk in PAH.
Adapted from the 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension.

Determinants of prognosis (estimated 1-year mortality)	Low risk 5%	Intermediate risk 5-10%	High risk >10%
Clinical signs of heart failure	Absent	Absent	Present
Progression of symptoms	No	Slow	Rapid
Syncope	No	Occasional syncope	Repeated syncope
WHO functional class	I,II	III	IV
6MWD	>440m	165–440mm	<165 m
Cardiopulmonary exercise testing	Peak VO_2 >15 ml/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44.[9]	Peak VO_2 <11 ml/min/kg (<35% pred.) VE/VCO_2 ≥45
NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/ml	BNP 50–300 ng/l NT-proBNP 300–1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18–26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
Haemodynamics	RAP <8 mmHg CI ≥2.5 l/min/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 l/min/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 l/min/m^2 SvO_2 <60%

TREATMENT OVERVIEW

It is important to start treating PAH as early as possible. Treating your PAH as directed by your doctor can help keep your PAH from getting worse.

While your medicine is working to help you, you can focus on the things you want to do, not your PAH. Set goals for yourself to remain active and enjoy important events with your family and friends. Looking forward to these things will help you stay positive.

BEING PRESCRIBED MORE THAN ONE MEDICINE

There are many kinds of treatments and medicines for PAH and each one may work differently. To help you get the best quality of life possible, your doctor may give you one or more medicines. Adjustments in your treatment do not necessarily mean something is wrong. It may just be required to optimise your treatment. It is important to take care of yourself and take the medicine or medicines prescribed by your doctor.

DIFFERENT APPROACHES

A number of treatment approaches may be used to treat your PAH, including:

- Oral therapy – pills that are swallowed
- Inhaled therapy – medicines that are breathed in through the mouth
- Medicines that are delivered continuously to the bloodstream through a vein or a needle placed under the skin (intravenous or subcutaneous therapy)
- Surgery – including lung or heart-lung transplantation

CONVENTIONAL TREATMENTS

There are several treatments that can help relieve symptoms of PAH, including:

- Blood thinners to prevent clots
- Diuretics (also called water tablets) to reduce swelling
- Digoxin to increase the strength of your heart and slow your heart rate
- Supplementary oxygen to ensure your body has enough oxygen

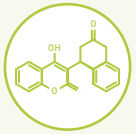
MEDICINES THAT TREAT PAH SPECIFICALLY

There are several medicines that treat PAH specifically. These medicines relax and widen the blood vessels in your lungs. They also reduce and prevent the overgrowth of cells in the walls of the vessels, which makes it easier for your heart to pump blood through your lungs. This should lead to an improvement in the level of your physical activity and well-being. These medicines include:

- Endothelin receptor antagonists (ERAs)
- Phosphodiesterase inhibitors (PDE5i)
- Prostacyclin analogues

CONVENTIONAL THERAPY

Conventional or supportive therapy is made up of treatments that most people living with PAH will be taking. These treatments include warfarin, diuretics (water tablets) and oxygen therapy.



WARFARIN

Warfarin is a drug called an anticoagulant. It is used to prevent blood clots forming within the blood vessels. Many people with PAH are at a greater risk of developing blood clots. These people are therefore given life-long warfarin, to protect them against developing clots. However, there are some people with PAH who should not to use warfarin, so your doctor will consider your situation and decide if warfarin is for you.

Because warfarin slightly reduces the ability of your blood to clot, it is worth taking a little extra care when doing exercise. Even minor injuries or knocks may result in bleeding or bruising.

The number of pills that you will need to take each day is different for different people. Your healthcare team will help determine the right dose for you. Other medicines that you may be taking can affect how well warfarin works. Because of this, you should always tell your doctor or pharmacist what medicines you are using before you start taking warfarin. This includes those bought without a prescription, and herbal medicines.

DIURETICS

Diuretics are often used in PAH to treat 'heart failure'. This term sounds very frightening, but does not mean that the heart has failed completely. Heart failure can be caused by PAH and means the heart is not working as effectively as it should.

Diuretics are commonly called 'water tablets'. They work by increasing the amount of urine you produce, which reduces the amount of fluid in the body. This decreases the pressure within the blood vessels.

Heart failure can cause fluid to build up around the lungs, causing shortness of breath. Diuretics are used to help the body

remove this excess fluid and relieve the symptoms of heart failure. By doing this, they make it easier for the heart to pump blood around the body.

There are several different types of diuretics and they are commonly given as tablets. Many, but not all people with PAH are prescribed diuretics. As diuretics cause people to produce more urine, many people prefer to take them in the morning rather than before going to bed, as this reduces the likelihood of needing to get up in the night to visit the toilet.

Common diuretics used are:

- furosemide (previously called frusemide)
- bumetanide
- metolazone
- spironolactone

People taking diuretics should have regular blood tests to monitor their kidney function.

DIGOXIN

Digoxin is another medicine often given to people whose heart is not working as effectively as it should. It works on heart cells to help maintain a normal, steady, and strong heartbeat.

Digoxin can be taken as a tablet or sometimes a liquid. The amount people with PAH need to take varies, depending on their weight, the health of their heart, and how they respond to the treatment. Your PAH doctor will work out the best dose for you.

Some other medications or food that has a lot of fibre can stop digoxin working effectively; your PAH team or pharmacist will explain when and how to take your medicine.

OXYGEN

People with PAH need their heart and lungs to work much harder to get the oxygen they need. PAH causes them to have too little oxygen in their blood while at rest or during exercise. This can lead to symptoms, such as tiredness and breathlessness. Oxygen therapy increases the amount of oxygen in the blood, and so can reduce these symptoms. Oxygen therapy may also improve concentration and the ability to do everyday tasks, such as walking short distances.

Oxygen therapy can be an important addition to treatment for PAH. As well as increasing the amount of oxygen in the blood, oxygen has the additional benefit that it is a vasodilator. This means that it helps to relax the arteries in the lungs, which can reduce the pressure in the pulmonary artery.

Oxygen can be obtained from:

- compressed oxygen cylinders
- liquid oxygen in cylinders
- an oxygen concentrator machine, which extracts oxygen from the air

If your doctor thinks you could benefit from oxygen therapy, your healthcare team will work with you to decide the best way for you to receive it at home.

TARGETED THERAPY

Targeted treatments work to address three key issues in PAH:

1 TOO MUCH ENDOTHELIN (ET).

Endothelin receptor antagonists (ERA) block the effect of too much ET. This helps relax and widen the blood vessels in your lungs, while also reducing the overgrowth of cells in the walls of the vessels.

2 NOT ENOUGH PROSTACYCLIN.

Therapies targeting the prostacyclin pathway work mostly by opening up blood vessels and by preventing the overgrowth of cells in the pulmonary arteries.

3 NOT ENOUGH NITRIC OXIDE (NO).

Phosphodiesterase type 5 inhibitors (PDE5i) and sGC stimulators increase the NO in the body. This helps relax and widen the blood vessels in your lungs, while also reducing the overgrowth of cells in the walls of the vessels.

1 TOO MUCH ENDOTHELIN (ET).

ENDOTHELIN RECEPTOR ANTAGONISTS (ERAS)

Endothelin is a substance that is made in the layer of cells that line the heart and blood vessels. It causes the blood vessels to constrict (become narrower). In people with PAH the body produces too much endothelin. This causes the blood vessels in the lungs to become narrow, increasing blood pressure in the pulmonary arteries.

ERAs work by reducing the amount of endothelin in the blood, which limits the harm it can cause. Opsumit® (macitentan) is an example of an ERA.

OPSUMIT® (MACITENTAN)

Opsumit® is an ERA that was specifically designed for the long-term treatment of patients with PAH. If you have been prescribed Opsumit® it is because your doctor thinks it is the best therapy for you.

Opsumit® was studied around the world in a large number of patients with PAH for up to 4 years. The study showed that Opsumit®:

- Helped patients live better lives by changing the course of the disease
- Improved patients' quality of life
- Helped patients to do more physical activity
- Relieved patients' symptoms
- Helped reduce the likelihood of hospitalisation due to PAH

Overall, the results of the study prove Opsumit® works well for people newly diagnosed with PAH. It also works well for people already taking PAH-specific treatment. It can be used alone or in combination with other common PAH medicines.

HOW OPSUMIT® CAN HELP YOU

Opsumit® can positively affect the course of PAH. This means that by taking Opsumit® you could spend more time doing the things you want to do in life with less interruption from your PAH.

WHO CAN TAKE OPSUMIT®?

Most people with PAH can take Opsumit® when prescribed by a doctor. Certain people should **NOT** take Opsumit®:

- Children below the age of 18 years should not take Opsumit®
- Women who are pregnant or plan to become pregnant during treatment should not take Opsumit®
- Women who are breastfeeding should not take Opsumit®
- People who are allergic to Opsumit® or any other ingredients in Opsumit® should not take Opsumit®
- People with liver disease or who have very high levels of liver enzymes in their blood should not take Opsumit®

If you belong to one of the above listed groups, please tell your PAH doctor.

HOW AND WHEN TO TAKE OPSUMIT®

GETTING STARTED

It is important that you read the Patient Information Leaflet (PIL) and patient card that comes inside your box of Opsumit®. Your doctor will also give you a patient card. The patient card explains possible side effects and risks to be avoided when taking Opsumit®. If you have further questions on the safety profile of Opsumit® please ask your PAH doctor.

Opsumit® is a tablet. You take it by mouth once a day. One tablet contains 10 milligrams (mg) of medicine. For best results, it is important that you take your medicine as your PAH doctor prescribed.

TAKING OPSUMIT® IS EASY

- Swallow 1 whole tablet with a glass of water
- Do not chew or break the tablet
- Take Opsumit® with or without food
- Take 1 tablet of Opsumit® each day
- It is best to take the tablet at the same time each day
- Choose a time that will help you remember, such as first thing when you wake up or when you brush your teeth

IT IS IMPORTANT TO TAKE YOUR MEDICINE EVERY DAY

If you forget to take Opsumit®, take a tablet as soon as you remember.

- Then continue to take your next tablet at your usual time
- Do **NOT** take a double dose (2 tablets at once) to make up for the forgotten tablet

OPSUMIT® SHOULD NOT BE STOPPED

- If you stop taking your medicine, this may cause your symptoms to get worse
- Do **NOT** stop taking Opsumit® unless you have agreed to this with your PAH doctor

DON'T LET YOUR MEDICATION RUN OUT

- If you do run out, contact your doctor or nearest PAH Centre as soon as possible
- They will help you set up a system to make sure you do not run out again

If you have taken more tablets than you have been told to take, ask your doctor for advice.

To get the most benefit it's important you take your Opsumit® every day. Stopping taking your medicine can cause your symptoms to get worse.

TAKING OPSUMIT® SAFELY

OPSUMIT® AND PREGNANCY

If you are pregnant or breastfeeding, think you may become pregnant, or are planning to have a baby, ask your PAH doctor for advice before taking this medication. Opsumit® may harm unborn babies conceived before, during, or soon after treatment.

- If it is possible you could become pregnant, use a reliable form of birth control (contraception) while you are taking Opsumit®. Talk to your PAH doctor about this
- Do not take Opsumit® if you are pregnant or planning to become pregnant
- If you do become pregnant or think that you may be pregnant while you are taking Opsumit®, see your PAH doctor immediately

If you are a woman who could become pregnant, your PAH doctor will ask you to take a pregnancy test before you start taking Opsumit® and regularly while you are taking Opsumit®.

WHAT IF YOU ARE LACTOSE INTOLERANT?

Opsumit® tablets contain small amounts of a sugar called lactose. If you have intolerance to lactose or any other sugars, you should speak with your PAH doctor before taking Opsumit®. Opsumit® tablets contain lecithin from soya. If you are allergic to soya, do not use this medicine.

BLOOD TESTS

As with all ERAs, if you are taking Opsumit® you will need to have regular blood tests to check that your liver is not being harmed by the drug. These blood test will often be done on a monthly basis. It ls important to realise as long as you have regular blood tests, it is extremely unlikely that the liver will suffer any permanent damage. It is therefore for your own safety that you have these regular blood tests.

PAH TREATMENTS LIKE OPSUMIT® MAY AFFECT YOUR LIVER

Watch for signs that your liver may not be working properly. If you notice any of these signs, **tell your PAH doctor immediately**.

- Feeling sick (nausea)
- Vomiting
- Fever
- Pain in your stomach (abdomen)
- Jaundice (yellowing of your skin or the whites of your eyes)
- Dark-coloured urine
- Itching of your skin
- Lethargy or fatigue (unusual tiredness or exhaustion)
- Flu-like syndrome (joint and muscle pain with fever)

2 NOT ENOUGH PROSTACYCLIN.

PROSTACYCLIN THERAPIES

Prostacyclins are powerful vasodilators that allow more blood to flow through the narrowed vessels in the lungs. This family of drugs work in a similar way to naturally occurring substances called prostaglandins produced by the body. Over time, by opening up narrowed vessels, strain on the heart is reduced. Successful treatment can result in significant shrinking and remodelling of the heart, helping it to work more efficiently again. Uptravi® (selexipag) and Veletri® (epoprostenol) are examples of a prostacyclin therapy.

UPTRAVI® (SELEXIPAG)

Uptravi® was specifically designed for the long-term treatment of patients with PAH. You may already be taking one or more different types of medicines for PAH. This does not always mean that your PAH is getting worse. Your doctor believes that Uptravi®, in addition to your other medicine(s), could be right for you.

HOW UPTRAVI® CAN HELP YOU?

Uptravi® can positively affect the course of PAH. In clinical studies, Uptravi® was found to reduce PAH-related hospitalizations and other PAH disease progression events. This means that by taking Uptravi® you could spend more time doing the things you want to do in life with less interruption from your PAH.

WHO CAN TAKE UPTRAVI®?

Most people with PAH can take Uptravi® when prescribed by a doctor. Certain people should **NOT** take Uptravi®:

- Children below the age of 18 years
- Women who are pregnant or plan to become pregnant during treatment
- Women who are breastfeeding
- People who are allergic to Uptravi® or any other ingredients in Uptravi®
- People with liver disease or who have very high levels of liver enzymes in their blood
- People who have any of the following conditions:
  - Poor blood flow to the heart muscles
  - Heart attack within the last 6 months
  - Weak heart that is not under close medical observation
  - Severe irregular heartbeat
  - Defect of the heart valves that causes the heart to work poorly

HOW AND WHEN TO TAKE UPTRAVI®?

GETTING STARTED

It is important that you read the Patient Information Leaflet (PIL) and patient card that comes inside your box of Uptravi®. Your doctor will also give you a patient card. The patient card explains possible side effects and risks to be avoided when taking Uptravi®. If you have further questions on the safety profile of Uptravi® please ask your PAH doctor.

Uptravi® is a tablet. You take it by mouth twice a day. Uptravi® comes in a range of dosage strengths. Your doctor will help you find the dosage that's right for you. For best results, it is important that you take your medicine as your PAH doctor prescribed.

DO NOT STOP TAKING UPTRAVI® WHEN YOU HAVE SIDE EFFECTS

Talk to your healthcare team when you have side effects.

- Your doctor may suggest medicines that can help relieve your diarrhoea, pain, nausea, and vomiting
- If you cannot tolerate side effects, even after your doctor has tried to treat them, they may recommend you step down to a lower dose

For most people, side effects go away or get better once they reach their individualised maintenance dose

FINDING THE DOSE THAT IS RIGHT FOR YOU

Once your doctor has started you on the lowest dose of Uptravi® (200 mg twice daily), he or she will slowly step up your dose over the next several weeks of treatment. This will help you get to the dose that is right for you. This process is called titration.

Your doctor will increase your dose, usually in weekly intervals. He or she may step down your dose if you are not able to tolerate the side effects. Once you reach your highest tolerated dose, it will be the dose you continue to take on a regular basis, unless your doctor tells you otherwise. This is called your maintenance dose.

If you belong to one of the above listed groups, please tell your PAH doctor.

TAKING UPTRAVI® IS EASY

- Swallow each dose of Uptravi® with a glass of water
- Do not chew or break the tablet
- Uptravi® is best taken with food
- Try to take your morning and evening doses at the same times every day

IT IS IMPORTANT TO TAKE YOUR MEDICINE TWICE EVERY DAY

- If you miss a dose of Uptravi®, take it as soon as you remember. If your next scheduled dose is due within 6 hours, skip the missed dose. Take the next dose at your regular time
- If you miss 3 or more days of Uptravi®, call your doctor to see if you need to change your dose
- If you take too much Uptravi®, call your doctor or go to the nearest hospital emergency room right away

UPTRAVI® SHOULD NOT BE STOPPED

- If you stop taking your medicine, this may cause your symptoms to get worse
- Do **NOT** stop taking Uptravi® unless you have agreed to this with your PAH doctor

DON'T LET YOUR MEDICATION RUN OUT

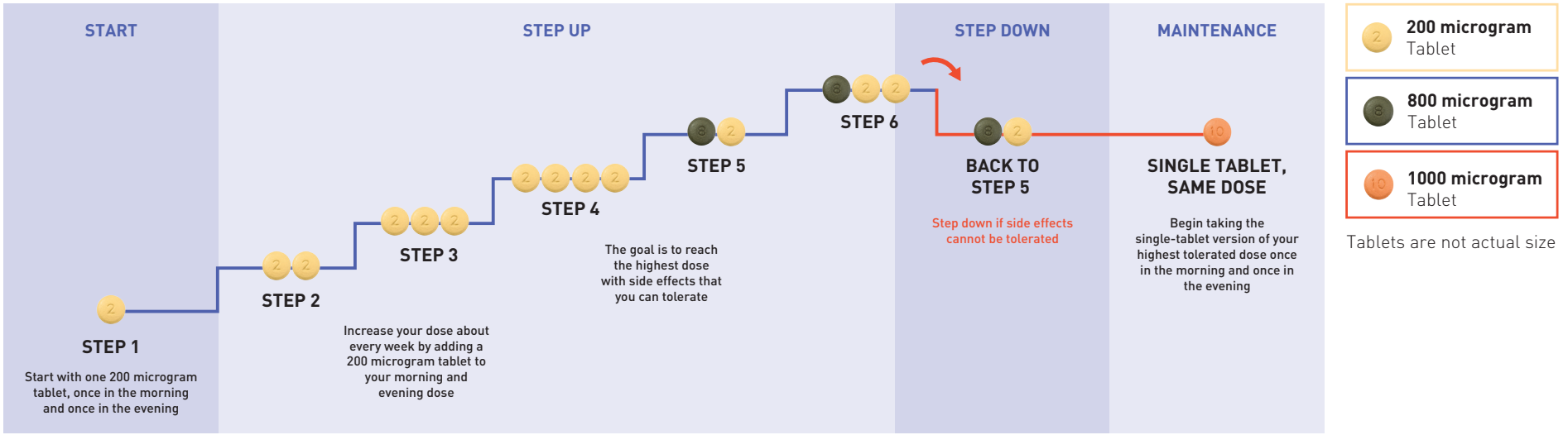
- If you do run out, contact your doctor or nearest PAH Centre as soon as possible
- They will help you set up a system to make sure you do not run out again

If you have taken more tablets than you have been told to take, ask your doctor for advice.

TAKING UPTRAVI SAFELY

Don't operate machinery or drive before knowing how your body reacts to Uptravi®, as Uptravi® can cause side effects, such as headaches and low blood pressure, which may affect your ability to drive.

HOW AND WHEN TO TAKE UPTRAVI®?



VELETRI® (EPOPROSTENOL)

Veletri® is a is a prescription medicine that is given intravenously (in a vein). When given continuously, Veletri® helps open up (dilate) blood vessels in the lung allowing blood to flow more easily.

HOW VELETRI® CAN HELP YOU?

Veletri® can help relieve some of the symptoms of PAH. In clinical studies, Veletri® was found to improve some people's ability to exercise, as measured by how far they could walk in 6 minutes.

WHO CAN TAKE VELETRI®?

If your doctor has prescribed Veletri® for your PAH, he or she believes it may help reduce your symptoms. You should not take Veletri® if you:

- Have heart failure due to severe left heart disease
- Develop fluid in the lungs (pulmonary edema) when starting therapy
- Are allergic to epoprostenol

Some medications may interact with Veletri®, so it's important to talk to your doctor about all of your medications.

HOW TO TAKE VELETRI®?

Veletri® is administered continuously for 24 hours via a portable pump. It is delivered through a very thin tube called a catheter into a large vein near the heart. One end of the catheter is surgically implanted in the chest while the other end is attached to a small, portable pump that holds your Veletri® in a reservoir called a cassette. Your pump should be on and you must carry or wear the pump at all times.

To avoid potential interruptions in your treatment, be sure to have access to a backup infusion pump and intravenous infusion sets, including a backup cassette.

FINDING THE DOSE THAT IS RIGHT FOR YOU

The amount of Veletri® you need on a continuous basis will be determined by your doctor and may change during your course of therapy. Your portable infusion pump will control the rate of medication you receive. Do not, on your own, abruptly lower your dose of Veletri® or stop taking it. All dose changes must be closely monitored by your doctor.

PREPARING AND STORING VELETRI®

Vials of Veletri® powder must be mixed (reconstituted) and then further diluted with commercially available Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. Veletri® should not be mixed with any other solutions or medications before or during administration. Each vial is for single use only; discard any unused solution.

You have the option to prepare and use your medicine immediately, or to prepare your medicine and store it in the refrigerator (2°C to 8°C) for up to 8 days.

TAKING VELETRI® SAFELY

Some people taking Veletri® experience side effects, including headaches, jaw pain, vomiting, nausea (feeling sick), diarrhoea, and redness in the face. Some side effects can be more serious. Tell you healthcare team immediately if you experience any of the following:

- Your heart is beating faster, or you have chest pain or shortness of breath
- You feel dizzy or feel faint, especially on standing
- You have fever or chills
- You have more frequent or longer periods of bleeding
- You see any sign of catheter site infection such as redness, pain, oozing or swelling around the insertion site

Remember, never change the way you prepare or store Veletri® unless instructed to do so by your healthcare professional.

3 NOT ENOUGH NITRIC OXIDE (NO).

PHOSPHODIESTERASE 5 INHIBITORS (PDE5I) AND SOLUBLE GUANYLATE CYCLASE STIMULATORS (SGCSS)

PDE5is and SGCs are classes of medicine that both work to increase the amount of nitric oxide (NO) in the body. This causes the blood vessels to relax and increases blood flow to the lungs and lowers blood pressure.

PREGNANCY AND PAH

Unfortunately, pregnancy and PAH is a dangerous combination. The life of both mother and child are put at great risk. Pregnancy puts a lot of strain on a woman's body, causing the heart rate to increase and the immune system to not be as effective, which combined with PAH is very serious. The risk of pregnancy-related death in women with PAH is between 25% and 50%.

In addition to the risk of PAH to the mother and child, some of the medicines used to treat PAH – such as warfarin – can also put the baby at risk. The multiple risks involved make pregnancy and PAH a complicated issue to address. PAH doctors agree that pregnancy should be avoided in women with PAH.

There are lots of very effective contraceptives that can be used safely in PAH, which your PAH team will be happy to discuss. Unplanned pregnancies can also occur and sadly, because of the risk involved, termination (abortion) needs to be seriously considered.

The advice at present is that pregnancy should be avoided in women with PAH.

WHAT IF I BECOME PREGNANT?

Some women who become pregnant decide to keep their baby even when they have been told of the very high risk involved. There are lots of new approaches to managing pregnancy in women with PAH but the risks still remain high. Early treatment and very careful planning can improve the chance of the mother surviving. Factors to improve the chance of survival include:

- being at the hospital early to prepare for the birth
- planned Caesarean section delivery
- careful use of anaesthesia during the delivery
- close cooperation of all members of the healthcare team including the PAH team, anaesthetists and obstetricians

However, even with extremely good care, the risk of pregnancy and PAH still remains high. It would be wrong to say that pregnancy and PAH can never have a successful outcome but it is important to get detailed, expert advice before making any decisions.

CONTRACEPTION AND PAH

Why do I need to use contraception?

It is recommended that pregnancy is avoided in women with PAH. If your PAH is secondary to another medical problem, such as systemic lupus, it is possible that the other problem may also reduce your chances of having a healthy baby. Contraception is therefore very important and should be discussed with your PAH team.

If you do become pregnant it is important for you to be seen by your PAH team as soon as possible, so they can discuss the options for treatment with you.

Which form of contraception should I use?

There are no guidelines for the use of contraception in PAH. However, some forms of contraception are more suitable for use in PAH so it is important to discuss contraception with your PAH team. Don't be embarrassed or avoid the issue - it is too important.

CAN I TAKE THE COMBINED PILL?

Oral contraceptive pills are a type of hormonal contraception. The combined pill, which is usually taken for 3 weeks out of every 4, should be avoided in women with PAH. This is because it contains oestrogen, which is thought to make PAH worse. It also slightly increases the risk of developing blood clots.

WHAT ABOUT PROGESTERONE - ONLY CONTRACEPTIVES?

The progesterone-only pill – also known as the minipill – is not recommended. This is because it must be taken at the same time each day, so is slightly less effective than the combined pill at preventing pregnancy.

Progesterone injection

Progesterone can be given by injection and is given every 8 or 12 weeks, depending on which type is used. This is a very reliable method of contraception. The progesterone injection can cause irregular bleeding in some women, although after a year of use most women stop having periods, which many see as an advantage.

Progesterone implant
An implant that releases progesterone can be fitted under the skin. The implant only needs replacing every 3 years, meaning women don't have to think about it at other times.

CAN I HAVE AN INTRAUTERINE DEVICE FITTED?

An intrauterine device or coil is a plastic or copper device that fits inside the womb. It is often difficult to fit a coil if someone has never been pregnant.

Many women with a copper-containing coil find their periods are heavier after it is fitted. This may already be a problem for you if you are taking warfarin. There is also a slightly increased risk of developing a pelvic infection. For these reasons, some doctors do not consider the coil as an ideal method of contraception for women with PAH.

There is also a progesterone-releasing intrauterine device, called Mirena. Many women using Mirena find after 6 months that their periods may last only 1–2 days. Mirena is a very reliable method of contraception, which lasts for up to 5 years.

WHAT ABOUT PERMANENT METHODS?

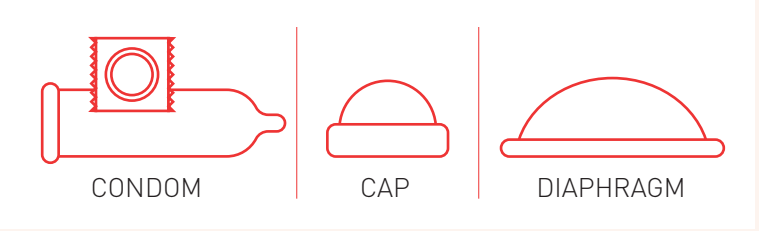
Male and female sterilisation are permanent methods of contraception. They are always an option, but the decision must not be taken before a great deal of very careful thought. It is very difficult to reverse the procedures.

Male sterilisation – called vasectomy – is the most reliable form of contraception. It has a very low failure rate once it has been confirmed as being successful.

Female sterilisation - involves an operation under general anaesthetic. This carries risks especially for women with PAH, particularly if you are on blood thinning drugs such as warfarin. Clips are used to block the tubes leading from the womb to the ovaries. There are no long-term side effects or risks, but there is a small failure rate.

ARE THERE ANY ALTERNATIVE METHODS OF CONTRACEPTION?

Barrier methods such as condoms, caps and diaphragms are less reliable. They should always be used with a spermicidal gel to reduce the chance of failure.



You should discuss the options for contraception with your PAH team and together decide the best method for you.

HRT AND PAH

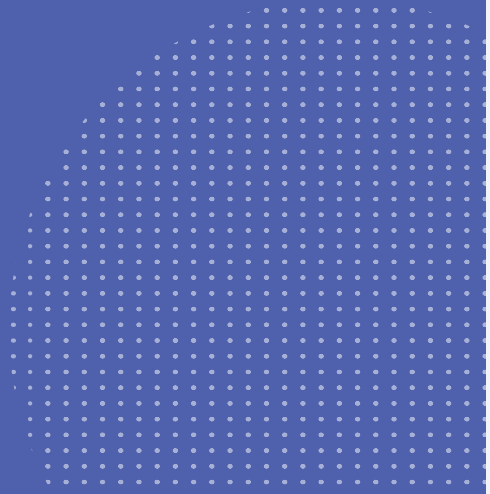
Hormone replacement therapy (HRT) is used to replace the hormones oestrogen and progesterone in women going through the menopause. It helps to improve symptoms such as hot flushes.

It is not very clear whether HRT should be used in postmenopausal women with PAH and many doctors believe HRT should only be used if symptoms, like hot flushes, are becoming intolerable.

LIVING WITH PAH

Living with and managing PAH symptoms can have an emotional impact. At times, you may feel low, frustrated, anxious, or may be unmotivated. It is important to know: **You are not alone.** These feelings are very common among people with PAH.

You can develop a support system to help you manage your condition. Your PAH team and local patient associations, together with the important people in your life, can be there when you need support.



SHARE YOUR THOUGHTS AND FEELINGS

People who do not know about PAH may not fully understand how you are feeling. To them, you may look and seem healthy. But underneath, you may be experiencing a range of feelings or limitations. By explaining the condition you have, the treatment plan you are on, and the changes you will make to your everyday life, you will give others a focus for managing their own feelings and supporting you.

TALKING ABOUT YOUR CONDITION

Although you may feel embarrassed to talk about PAH and its effects on your quality of life, talking to someone can be helpful. You may also find comfort in sharing your thoughts, feelings, and experiences with a friend or relative and with your PAH doctor or nurse. A good relationship with others allows you to discuss your concerns more easily. The more your support network knows and understands about you, the more they can help you.

TALKING TO PEOPLE WHO KNOW ABOUT PAH

If it is hard for you to talk to your family or friends about everything, ask your PAH doctor for help in finding someone in your area who you can talk to, like a social worker, counsellor, or psychologist. There are people who deal with PAH every day and can offer help and advice. Patient associations can be a great source of support and comfort in helping you with all aspects of day-to-day living with PAH.

ACCEPTING HELP FROM OTHERS

Don't be afraid to ask for help when you need it or accept help when it is offered. Accepting help gives those who care about you a sense of making a contribution at a difficult time. It can also allow you to get on with the things that you can and want to do.

Consider these ways in which others may help you:

Everyday support	Medical support
Running errands	Getting to doctor appointments
Preparing meals	Taking notes at doctor appointments
Doing household chores	Picking up medicine

SET GOALS AND MAKE ACTIVE CHOICES

There are many choices you can make to help maintain your health whilst living with the symptoms of PAH. Making these choices will help you to achieve the things you want.

Eating healthily, being active, learning how to cope with tiredness, and sharing your feelings are just some of the things that can make a big difference to how you feel and how you adjust to living with PAH.

HEALTHY EATING

There is no set diet to help to reduce PAH symptoms, but it is important to eat normally and healthily to keep your energy levels up. You should aim to achieve and stay at a healthy weight. If you notice any significant weight loss or gain, tell your PAH doctor. For a healthy diet consider:

- Changing to a salt-free diet
- Avoiding packaged and prepared food as these are often high in salt, fats, and sugar
- Eating smaller, more frequent meals
- Eating fresh fruit, vegetables, and whole grains
- Eating fish and lean meat, such as chicken

Drinking alcohol may be acceptable in moderation. Some foods and drinks can affect medicines, so you need to check with your PAH doctor if there is anything you should avoid.

STAYING ACTIVE

It may be hard to know how much or what type of exercise is possible with PAH. With help from your PAH team, you can figure out the level of activity that is right for you. Choose activities that you enjoy and that make you feel good. Here are some helpful tips:

- Start out slow and listen to your body
- Have enough breath to be able to talk
- Adjust your activity before you become tired
- If you experience any symptoms that concern you, for example dizziness or chest pain, seek medical advice

If you have any concerns or simply want to have reassurance that you are doing the right amount of activity, speak to your PAH team. Gym instructors, personal trainers, or people with similar jobs may not understand how PAH can affect an individual, so your best source of advice will be your PAH doctor and healthcare team.

MANAGING TIREDNESS

A common symptom of PAH can be extreme tiredness. This is caused by a decreased supply of oxygen to the body. It may feel different than feeling run down or tired from lack of sleep. Getting to know your body and understanding the signs it gives are important. This will enable you to rest when your body needs it.You may find that certain activities, times of the day, or particular emotions (like stress or anxiety) tend to trigger fatigue.

Keeping notes or a diary of when you have felt particularly tired will help you to notice, and then avoid, specific triggers. A diary can help you know the times you are at your best and which activities use the most energy. This can help you adapt to situations and plan for both your everyday activities and the bigger events in your life.

CHILDREN AND PAH

Children and babies can also have PAH. Doctors use the same sorts of tests as on adults to make a definite diagnosis and rule out other conditions. However, treatment plans can be very different for children

Children with PAH are often tired a lot, become breathless when they exercise, and their lips and fingernails might be slightly blue. They are also more likely than adults to get dizzy and faint. They might have a hard time keeping up with other children because of tiring easily. Children with PAH can also fail to put on weight.

TREATMENT

Treatments that are used in adults with PAH are also effective in children. However, because children change more quickly than adults, they have to be watched closely by the PAH team. This approach allows treatment to be adjusted according to how the child is responding, which helps to improve quality of life. With the correct treatment, children appear to have a better long-term outlook than adults. Lung transplantation may be an option for severe PAH if other treatments have failed.

There are a few things that should be considered if you have a child with PAH:

- If you are unsure about any medication another non-PAH doctor has prescribed your child, contact your PAH team
- Do not allow your child to have a general anaesthetic before the anaesthetist has talked to your PAH team
- Make sure your dentist knows your child has PAH

COPING WITH PAH

When a child has PAH it can affect the whole family. It's normal for family members to feel fed up and worried by the disease at times. It may be hard, but you should try to treat any child with PAH as normally as possible. Try hard not to forget other children in the family; they may feel upset at the extra attention that their brother or sister is being given. Make sure that friends and family are aware of the need not to pay less attention to your other children and ask that they treat them as equal.

As with any sick child, behavioural problems can crop up from time to time. For example, children can be more demanding than usual when leaving hospital. This is quite common, so you should be ready for it. Children just out of hospital can be clingier or may revert to earlier behaviours such as bedwetting. Again, just ask your PAH team for help or advice if you think you need it.

Points to remember about children and PAH

- Children often respond better to treatment for PAH than adults
- Keeping your children's lives as normal as possible will make them happier
- A child with PAH can still do lots of different activities
- Keep in close contact with your child's PAH team and ensure your GP is up to date on your child's condition and treatments
- If you are unsure about anything, contact your PAH team

NOTES

NOTES

NOTES