

Public information

Overview of Pulmonary Hypertension medications

Tracleer (Bosentan)

Tracleer was the first oral medication to gain a licence specifically for the treatment of PH in 2001. Tracleer is part of a class of medications called endothelin receptor antagonists or ERA's. It has been used and studied in children and appears to be safe.

How does it work in PH?

Endothelin is a chemical messenger normally found within the body. Endothelin is made by the body in the endothelium (a layer of cells which line the heart and blood vessels). Endothelin constricts blood vessels and increases blood pressure. Endothelin is a very powerful vasoconstrictor that plays an important role in blood flow. In PH, the body produces excess endothelin, contributing to the constriction of blood vessels and affecting the blood pressure in the lungs. It is one of the chemicals involved in the overall control of blood vessel activity. Although endothelin is present in healthy people, high concentrations of the substance have been found in the plasma and lungs of patients with PH suggesting that it plays a part in keeping the pressure in the lungs high.

The blood vessels in the lung need to be able to adapt to the changing needs of the body in order to maintain balance/health. For the body to achieve this it needs to produce some chemicals that cause the vessels to open up and some that cause them to become narrow. In other words endothelin is not a bad chemical that harms the body, but too much of it is not a good thing!

Using a traffic jam analogy, PH is the equivalent of rush hour on the M25. Despite clear road signs and speed cameras, the system cannot cope with such increased demands. Treatment with ERA drugs is like adding another lane to the M25. Whether or not this will solve the root cause of the problem or whether it will simply act as a short-term pressure release is yet to be seen.

Endothelin causes blood vessels to narrow and can also aggravate scarring and overgrowth of the muscle in the walls of blood vessels in the lungs.

By blocking the action of endothelin, Tracleer can lead to a reduction in the blood pressure in the lungs and to improvement in activity levels and well-being. While improved exercise capacity and increased sense of well-being have been seen in short-term studies of Tracleer, there is less information regarding long-term effects.

Tracleer - are there any side effects?

Reported side effects include nasal congestion, headache, increased blood flow to the skin on the face (facial flushing) and swelling in the legs. It is also thought to have some interaction with warfarin requiring an increase in the dose necessary to maintain the effectiveness of warfarin.

The major potential side effect is liver problems. The development of abnormal liver function tests (which are measured by a simple blood test) is seen in about 7-10% of adults. This side effect is less common in children. It is important to know that it has now been given to thousands of patients without any reports of permanent liver damage. It is

important that patients have regular (normally monthly) blood tests to measure its effects on the liver.

It is also believed that Tracleer can decrease the effectiveness of hormonal contraceptives (e.g. the contraceptive pill) and such hormonal contraceptives should not be used alone for the prevention of pregnancy during treatment with Tracleer. In animal studies, Tracleer has been shown to be harmful to the growing foetus, therefore it is very important that women being treated with this drug avoid becoming pregnant.

2. Revartio (Sildenafil /Viagra)

Viagra was, to a large extent, discovered by chance. It was initially developed to treat patients who had heart disease, such as angina. During the early clinical trials, an unexpected “side effect” was discovered – that this medicine could improve and maintain a man's erection. Hence why Viagra tablets are most commonly known for their use in the treatment of erectile dysfunction (impotence)

However, Viagra only promotes penile erection in response to sexual stimulation and has no effect in its absence. Therefore, if a healthy man takes Viagra and occupies himself with his usual daily activities, he would not be expected to develop an erection within the five or six hours in which the medicine is active unless sexual stimulation took place.

It was as long ago as 1998 (when Viagra first came onto the market) that its use was first considered in PH. Doctors knew enough about this medicine and how it worked to consider it as having a positive potential use in the treatment of PH.

How does it work in PH?

This may sound like a rather complex process, but read it through a few times and you'll get it!

Viagra causes the relaxation of the smooth muscle in the blood vessels which in turn has the effect of increasing blood flow. It does this by blocking a particular enzyme (an enzyme is a protein that assists chemical reactions to take place) called “phosphodiesterase type 5” (often abbreviated to PDE 5).

A complex chain of events, involving signals from the nervous system and the release of chemical messengers within the tissues takes place. One of these chemical messengers is called “cyclic GMP”. Cyclic GMP causes the blood vessels to widen by relaxing the thick layer of muscle found in the blood vessel walls.

Cyclic GMP is normally broken down in the body by PDE 5. Viagra works by inhibiting the action of PDE 5, thus stopping the breakdown of cyclic GMP. This means that the blood vessels are kept dilated for longer, improving blood flow.

The use of Viagra in the treatment of PH

A recent clinical trial has just been completed looking at the effectiveness of using Viagra in the treatment of PH. It looks very likely that this clinical trial will be successful and will show that it can improve exercise capacity in some people with PH. The European agency that gives pharmaceutical companies their licenses for medicines is likely to grant Pfizer (manufacturers of Viagra) a licence for the treatment of PH early in 2006. It is proposed (and fully supported by the PHA-UK) that this medicine should only be initiated and monitored by doctors experienced in the treatment and monitoring of patients with PH. Pfizer are intending to market Viagra for the treatment of PH by giving it a specific new brand name, Revatio. The usual dose will be one tablet (20mg) three

times a day. However, the PH specialists may alter this dose according to people's response to the medicine.

Viagra - are there any side effects?

Medicines can affect individual people in different ways. The following are some of the side effects that are known to be associated with Viagra. Just because a side effect is stated here, it does not mean that all people taking this medicine will experience that or any side effect.

Headache

Increased blood flow to the skin on the face (facial flushing)

Dizziness

Visual disturbances, such as blurred vision, blue tinge to vision

Nasal congestion

Awareness of your heart beat (palpitations)

Indigestion

Abnormal heart beats (arrhythmias)

Low blood pressure (hypotension)

High blood pressure (hypertension)

Fainting or feeling you might faint

Nose bleeds

Rash

Chest pain

It should be remembered that much of the experience gained with this medicine has been based on smaller dosages used for erectile dysfunction and not for the bigger doses that are going to be used in PH. Reassuringly though, the clinical trial in PH did not show any major problems in these higher dosages.

It is very important to tell your doctor or pharmacist what medicines you are already taking, including those bought without a prescription and herbal medicines, before you start treatment with this medicine. Similarly, check with your doctor or pharmacist before taking any new medicines while taking this one.

For more information about any other possible risks associated with this medicine, please read the information provided with the medicine and talk to a pharmacist, PH specialist nurse or PH doctor.

Viagra must not be taken with any form of nitrate medication, as this combination can produce a severe drop in blood pressure that can cause dizziness, fainting, or even a heart attack. Nitrate medications include the following:

Glyceryl trinitrate, isosorbide mononitrate and isosorbide dinitrate (used for angina or heart failure)

Nicorandil (used for angina)

Amyl nitrate (also known as "poppers")

Viagra - Long term use in PH

The use of Viagra in PH is relatively recent and its long term benefits remain to be seen, but the outlook is positive. It is another weapon in the armoury of the treatment of PH. Importantly too, it is far cheaper than all the other treatments used in PH. The high cost

of PH treatments can be a significant dynamic in healthcare management plans and hopefully this should help lessen the financial burden. This lower cost also makes it much more realistic and possible for the PH specialist to consider using it in combination with other medicines. That said, it must be remembered that there is little evidence of either benefits or risks at present for the use of combination therapy and it will not be appropriate for everyone with PH.

3. Calcium Channel Blockers



Calcium channel blockers (CCB's) are oral medications which relax the muscles around blood vessels. They also have an effect on the electrical system of the heart by regulating fast heart rates. These types of drugs are therefore commonly used to treat angina type pain as slowing the rate at which the heart beats means the heart uses less energy and the pain of angina is prevented or relieved. As CCB's also have a mild widening effect on blood vessels they also reduce blood pressure.

Who can take CCB's?

Unfortunately, less than 10% of people with PH are "responders" to CCB's. CCB's are also prescribed for systemic hypertension (high blood pressure), but in much lower dosages than when they are prescribed for PH.

Depending on the specific medication and the dose, they may be taken from one to three times a day. Some CCB's come in intravenous form as well and are used in hospitalised patients to control heart rate and blood pressure. The CCB's used most frequently in patients with PH are:

Nifedipine and nicardipine
Diltiazem
Amlodipine

While early studies supported more widespread use of CCB's for treatment of PH, it now appears that they are beneficial in only a small subset of PH patients. These patients are those who have demonstrated a very good response to vasodilator testing during right heart catheterisation.

This type of medication should be taken at regular times each day. If a dose is missed by mistake a double dose should not be taken the next time. It is also very important that this drug is not suddenly stopped and that the PH specialist team is fully aware if any other doctor wants to stop it.

CCB's - are there any side effects?

All medicines and their possible side effects can affect individual people in very different ways. The following are some of the side effects that are known to be associated with CCBs (whichever type is being taken). Because a side effect is stated it does not mean that all people using this medicine will experience that or any side effect.

Slower than normal heart beat
Increased blood flow to the skin on the face (facial flushing)
Awareness of heart beat (palpitations)
Low blood pressure

Headache
Dry mouth
• Nausea
Ankle swelling
Dizziness or loss of balance

4. Prostacyclins

Prostaglandin is a type of steroid that is made naturally by the body. There are different types, which all have different roles to play. It causes blood vessels in the lungs to relax and allow blood to flow through them more easily. People with pulmonary hypertension do not produce enough prostaglandin, so the blood vessels in the lungs are constricted. Prostacyclins are a group of chemicals that are administered to remedy this deficiency. This chemical can be synthesised (made artificially) by drug companies. Although research continues on other forms of prostacyclins, it is currently available in three forms:

Flolan (Epoprostenol)

Ventavis (Iloprost)

Remodulin / UT-15 (Treprostinil)

All these drugs are powerful substances. Prostacyclins are not suitable for all patients. All of these require a great deal of specialist support, management and training to use them effectively and safely. The following therefore only gives an overview of each treatment.

Flolan (Epoprostenol)

This therapy was first used for the treatment of pulmonary hypertension in 1985 and it is the treatment with which the PH specialist teams have the greatest long term experience. It helps relax the blood vessels in the lungs and slows the process of scarring and cell growth within blood vessels, which prevents further narrowing. It also assists in increasing cardiac output and oxygen saturation of the blood. It has been shown in a number of studies to prolong survival, improve quality of life and improve oxygen tolerance. Flolan was first used as a "bridge treatment" prior to transplantation, however, it has now emerged as a good and effective alternative to transplant. It is a treatment that is commonly reserved for PH in its most advanced form.

How is it administered?

Flolan is administered intravenously (directly into the bloodstream). A permanent, surgically implanted catheter is placed in one of the large veins going to the heart. In the UK this catheter is often referred to as a Hickman line. It must be given this way because this drug lasts for only a very short time (3-5 minutes) in the bloodstream. A portable, battery-operated pump that administers the Flolan is worn attached to a belt around the waist or carried in a small shoulder pack. Smaller children usually use a secure backpack. A thin plastic "cannulae" connects the pump to the catheter. The drug comes as a powder and needs to be mixed in a very specific and exact way. The care and long term management of Hickman lines requires a very high level of cleanliness to reduce the risk of serious infection. It is a treatment that must be started in hospital with highly experienced PH team members to help teach the individual or, in the case of children the

parents or carers, all the complexities involved. This can require a 10 - 14 day hospital stay.

Maintenance

Flolan is freshly mixed each day and stored in a plastic cassette or syringe, which is attached to the pump. The dosage of Flolan changes frequently, especially in the early stages of treatment. The PH team determines the dosage, which is influenced by the response of the individual to the treatment.

Flolan - are there any side effects?

Side effects of Flolan can include jaw pain, headache, flushing, nausea, diarrhoea and vomiting but many of these subside over a short period of time. Sunlight sensitivity can also develop in some people. Hickman line infections occur occasionally and are of a serious concern. A line infection requires hospitalisation, intravenous antibiotics and sometimes replacement of the line. Individuals on this treatment are taught how to recognise the early signs of a possible infection.

Summary

Flolan is a treatment that is used in both adults and children. The treatment is complex and requires a significant degree of dexterity and understanding to administer. The risk of infection (which can be life threatening if not managed quickly and appropriately) is a constant concern. It is not a treatment that is ever embarked upon lightly nor is it appropriate for all. As this is a permanently placed line and involves wearing a small portable pump many people need support, reassurance and help with issues about their own body image. Nonetheless, it can be a life saving and life enhancing treatment when used with the right support and back up.

It is not known if there are problems with using this drug in pregnancy but it has not been shown to cause birth defects or other problems in animals. It is not known if it is excreted in breast milk. It is crucial to remember that pregnancy and PH is a very high risk situation for both the mum and the baby regardless of what treatment is given.

Ventavis (Iloprost)

Ventavis is a liquid containing a drug called Iloprost that, until recently was only given intravenously for the treatment of PH. Now, Ventavis can be used as an inhaled medication that acts in the same way as prostacyclin (relaxing blood vessels to help stop them becoming narrowed or blocked, increasing cardiac output and oxygen saturation, improving exercise tolerance and prolonging survival and quality of life). Ventavis helps more blood get to the lungs and helps to collect oxygen. This tends to lower blood pressure in the pulmonary artery which should in turn put less strain on the heart.

How is it administered?

Ventavis is inhaled into the lungs using a “nebuliser” (a device that changes the Ventavis liquid into a fine spray or mist). It can take about 10 minutes to nebulise each dose of Ventavis and the effects last for one or two hours. Because this effect is only for a limited time, it is necessary to take Ventavis 6 or 7 times a day usually every three hours. The first dose of the day will therefore often need to be taken as early as 6.00am, which isn't good for those who like a lie in! This frequency can be very inconvenient for some individuals, but it is crucial not to cut out doses because the beneficial effects are much

reduced or completely lost. The nebuliser machines need to be well maintained and kept clean and in good working order.

The care and long term management of the nebuliser and dosing regime requires a good level understanding and motivation on the part of the individual commencing treatment. It must be started in hospital with highly experienced PH team members to help teach the individual all the complexities that are involved. This can require a 3 - 5 day hospital stay.

In the UK some PH patients, under the supervision of the PH specialist teams, use Iloprost in the very same way as Flolan and it is delivered intravenously through a Hickman line. It is used instead of Flolan because it is generally easier to manage as the medication doesn't require it to be mixed from powder form and it is a little more stable.

Ventavis - are there any side effects?

Side effects of Ventavis can include a troublesome cough, jaw pain, nausea, diarrhoea, headache or facial flushing at the time of taking Ventavis and occasionally vomiting. Sunlight sensitivity can also develop in some people.

Summary

Inhaled Ventavis is an effective treatment for PH, it is often used for the less severe forms of PH and for those patients in whom other forms of prostacyclin cannot be used. The main problem though is the need to use it as much as 7 times a day. This is often not a suitable treatment for individuals with busy lives either with work, family or school. Similarly to the other prostacyclins, it is not known if there are problems with using this drug in pregnancy but it has not been shown to cause birth defects or other problems in animals.

Remodulin (Treprostinil)

Remodulin (often referred to as UT-15, its name during clinical trials) is a synthetic, more stable form of prostacyclin than Flolan. Remodulin is stable at room temperature for up to five years. The drug's dilation action lasts from 2 - 3 hours compared to the short 2 - 3 minute action of Flolan. Just like Flolan it relaxes the blood vessels in the lungs and slows the process of scarring and cell growth within the blood vessels, which prevents further narrowing. It also assists in increasing cardiac output and oxygen saturation, improves exercise tolerance and prolongs survival and quality of life.

How is it administered?

Remodulin is administered subcutaneously (which means, under the skin) rather than into the bloodstream. This significantly lowers the risk of infection and related hospitalisations associated with the Hickman line. There is ongoing work with this drug to look at its effective use if given intravenously in the same manner as Flolan and intravenous Iloprost. There are also investigations being done in the area of a potential inhaled form of Remodulin.

Remodulin is delivered by a "Mini-Med portable infusion pump", a pump about the size of a mobile phone. Patients learn to insert the catheter under the skin themselves, this is called the "infusion site". Most patients will use each infusion site for around 3 days although some use it for longer. Remodulin does not require mixing as the fluid comes in ready-to-use glass vials. No refrigeration is needed. A small syringe is used to withdraw the solution and the syringe itself becomes the cassette placed into the pump. The care and long term management of the pump and infusion site requires a good level of

cleanliness to reduce any small risk of localised infection. The treatment must be started in hospital so the PH team members can teach the individual all the complexities involved. This can require a 3 - 5 day hospital stay.

Remodulin - are there any side effects?

The main drawback of Remodulin is site pain, which for some patients can be quite severe. Often a pain medication has to be prescribed for Remodulin patients. The reason some people get pain and others don't is not understood. However, of those who do experience pain and persevere with the treatment, it often seems to wear off completely over time or at least become much less troublesome. This pain is not due to the needle being injected, it is thought to be due to the drug irritating nerve endings. Site pain can be so severe that about 25 - 50% of patients have to stop the treatment. This type of therapy is relatively new when compared to Flolan and there is not as much long term data on its effectiveness.

Remodulin can also have the same side effects as Flolan, but they are often not as severe. These can include jaw pain, headache, facial flushing, nausea, diarrhoea and vomiting. Sunlight sensitivity can also develop in some people.

Summary

When given subcutaneously, Remodulin appears to be as effective as Flolan for treating PH. The main problem however is the potential site pain. Inhaled forms of this drug may however be available in the next few years.

Similarly to the other prostacyclins, it is not known if there are problems with using this drug in pregnancy and it has not been shown to cause birth defects or other problems in animals. It is not known if it is excreted in breast milk.

5. Warfarin



This is a drug called an anticoagulant and it is used to help prevent blood clots forming within the blood vessels.

Blood clots normally only form to stop bleeding that has occurred as a result of injury to the tissues. The clotting process is complicated and begins when blood cells called platelets clump together at the site of damage and produce chemicals that activate clotting factors in the blood. This is the body's natural way of repairing itself.

Sometimes, however, a blood clot can form abnormally within the blood vessels. This is known as a thrombus and can be dangerous because the clot may detach and travel in the bloodstream, where it becomes known as an embolus. It may eventually get lodged in a blood vessel, thereby blocking the blood supply to a vital organ such as the heart, brain or lungs.

Some people have an increased tendency for blood clots to form within the blood vessels. This is usually due to a disturbance in the blood flow within the blood vessels. For example:

Fatty deposits on the walls of the blood vessels (atherosclerosis) can disrupt the blood flow, giving a tendency for platelets to clump together and start off the clotting process. Slow blood flow in the leg and pelvic veins can also result in clots forming (deep vein thrombosis). These clots can break off and travel to the lungs (pulmonary embolism).

Warfarin is used to reduce the risk of blood clots forming inside the blood vessels in conditions such as these.

How does it work?

Warfarin works by inhibiting the action of vitamin K which prevents the production of the clotting factors. Without these clotting factors blood clots are less likely to occur. It takes about three days for clotting factors that have already been produced to be used up and therefore the full anticoagulant effect of warfarin is not seen immediately. For this reason, when treating blood clots such as deep vein thrombosis (DVT) or pulmonary embolism, a faster acting anticoagulant that can be injected, such as a heparin, is often used as well.

The anticoagulant effect of warfarin is measured in the time it takes for blood clotting to occur in a sample of blood. This time is expressed as the International Normalised Ratio (INR). Regular blood samples are taken from the patient (normally 4 - 8 weeks apart) to allow for adjustments to the dose as necessary to make the INR fall into the range shown to be effective at preventing blood clots in that particular condition. In PH this range is commonly between 2 and 3. It is therefore important that the PH patient has regular blood tests to monitor their blood clotting ability (INR) so the dose can be altered if necessary. It is worth taking a little extra care when participating in physical activities while on this type of medicine, as even minor injuries or knocks may result in an increased chance of bleeding or bruising.

Consult your doctor immediately if you experience any of the following while on this medication:

- Prolonged bleeding from cuts
- Bleeding that does not stop by itself
- Nose bleeds
- Bleeding gums
- Red or dark brown coloured urine
- For women, increased bleeding during periods (or any other vaginal bleeding)

The anticoagulant effect of warfarin can be affected by many medicines. You should always tell your doctor or pharmacist what medicines you are using, before you start treatment with this medicine. This includes those bought without a prescription and herbal medicines. Likewise, check with your doctor or pharmacist before starting any new medicines while you are taking this medicine, or other medicine.

6. Diuretics



Diuretics are commonly called 'water tablets'. They work by stimulating the kidneys to increase urine output. There are several different types of diuretics and they are commonly given in tablet form. Many, but not all patients with PH are prescribed diuretics. Diuretics work by causing the kidneys to increase the amount of salt and sodium that is filtered out of the blood and into the urine. When these salts are filtered out of the blood by the kidneys, water is also drawn alongside (like a magnet).

Removing water from the blood decreases the volume of fluid circulating through the blood vessels. This subsequently decreases the pressure within the blood vessels. As diuretics remove fluid from the body, they are used to treat conditions where excess fluid has been retained in the body (known by the medical term 'oedema'). In PH, the heart

often does not work as effectively as it should. This is often called "heart failure", which can sound a bit dramatic and frightening, but it should be remembered that it does not mean the heart has failed, just that it is not working as effectively as it should. Heart failure is a disorder in which the heart loses its ability to pump blood efficiently throughout the body. The oxygen and nutrients in the blood provide the body with the energy it needs to operate efficiently.

The effects of this are, for example, that fluid can accumulate around the lungs, causing shortness of breath. Diuretics are used to help the body remove this excess fluid and therefore relieve the symptoms of heart failure. The decreased pressure in the blood vessels caused by the diuretic also decreases the effort required by the heart to pump blood around the body, which is useful in heart failure where the pumping mechanism of the heart is less effective. This excess fluid may also accumulate in the abdomen or in the legs.

As diuretics cause the kidneys to produce more urine, many people prefer to take this medicine 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 (previous called Frusemide)

Bumetanide

Metolazone

Spirolactone

Diuretics - are there any side effects?

People taking this type of medicine should have regular blood tests to monitor their kidney function. Any of the following symptoms should be reported to the doctor promptly, so that the amount of fluids and salts in the patient's body can be checked: excessive thirst, lethargy, confusion, weakness, drowsiness, muscle cramps, lower than normal production of urine, feeling sick and vomiting.

Some patients may experience fatigue when first taking this medication, but this usually passes after they have been on the medication for some time. As the amount of urine flow will increase, patients may need to wake during the night to urinate. To minimize this, patients with a single daily dose should take their medication in the morning after breakfast. Patients taking more than one dose a day are advised to take their last dose before 6.00pm. Some diuretics can also increase the skin's sensitivity to sunlight. It is therefore advisable to use sunscreen and avoid tanning booths. Furthermore, patients being treated for pulmonary hypertension may be advised to weigh themselves frequently and report any loss or gain of more than 2 - 3 kg (about 5 lbs) in a week. It is important to do this weighing at the same time of the day and after going to the toilet to empty your bladder.

Medicines and their possible side effects can affect individual people in different ways. It is very easy to become over concerned about the mention of side effects. Because a side effect is stated here, it does not mean that all people using this medicine will experience that or any side effect.

Headache

Thirst

Disturbed sleep

A drop in blood pressure that occurs when going from lying down to sitting or standing, which results in dizziness and light-headedness

Fatigue

Disturbances of the gut such as diarrhoea, constipation, nausea, vomiting or abdominal pain

Dizziness

Loss of appetite

Disturbances in the levels of chemical components (electrolytes) in the blood

A general feeling of being unwell (malaise)

Rash or itching

Inhaled Iloprost – Frequently asked questions

Q. *How does the molecular structure of iloprost compare to endogenous prostacyclin?*

A. Iloprost is a synthetic analogue of prostacyclin (PGI₂) and is structurally similar to endogenous prostacyclin.

Q. *What is the plasma half-life of iloprost?*

A. The plasma half-life of iloprost is 20 to 30 minutes. Following inhalation of iloprost (5.0 mcg), patients with pulmonary hypertension have iloprost peak serum levels of approximately 150 pg/mL. Iloprost was generally not detectable in the plasma 30 minutes to 1 hour after inhalation.

Q. *Does cytochrome P450 play a role in the biotransformation of iloprost?*

A. *In vitro* studies reveal that cytochrome P450-dependent metabolism plays only a minor role in the biotransformation of iloprost.

Q. *Can any significant drug interactions be expected with Ventavis?*

A. In studies in normal volunteers, there was no pharmacodynamic interaction between intravenous iloprost and either nifedipine, diltiazem, or captopril. However, iloprost has the potential to increase the hypotensive effect of vasodilators and antihypertensive agents. Since iloprost inhibits platelet function, there is a potential for increased risk of bleeding, particularly in patients maintained on anticoagulants.

During clinical trials, iloprost was used concurrently with anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, corticosteroids, and other medications. Intravenous infusion of iloprost had no effect on the pharmacokinetics of digoxin. Acetylsalicylic acid did not alter the clearance (pharmacokinetics) of iloprost. Although clinical studies have not been conducted, *in vitro* studies of iloprost indicate that no relevant inhibition of cytochrome P450 drug metabolism would be expected.

Q. *What was the primary efficacy endpoint in the Ventavis Phase 3 clinical trial?*

A. The primary efficacy endpoint was clinical response at 12 weeks, a three-part composite endpoint defined by

- improvement in exercise capacity (6-minute walk test) by at least 10% versus baseline evaluated 30 minutes after dosing, and
- improvement by at least one NYHA Class versus baseline, and

c) no death or deterioration of pulmonary hypertension.

Deterioration required two or more of the following criteria

- 1) Refractory systolic blood pressure <85 mm Hg
- 2) Worsening of right heart failure with cardiac edema, ascites, or pleural effusion despite adequate background therapy
- 3) Rapidly progressive cardiogenic hepatic failure (e.g., leading to an increase of GOT or GPT to >100 U/L, or total bilirubin ≥ 5 mg/dL)
- 4) Rapidly progressive cardiogenic renal failure (e.g., decrease of estimated creatinine clearance to $\leq 50\%$ of baseline)
- 5) Decrease in 6-minute walk distance by $\geq 30\%$ of baseline value
- 6) New long-term need for I.V. catecholamines or diuretics
- 7) Cardiac index ≤ 1.3 L/min/m²
- 8) CVP ≥ 22 mm Hg despite adequate diuretic therapy
- 9) SVO₂ $\leq 45\%$ despite nasal O₂ therapy

Q. *Are there any trough efficacy data available for the effect of Ventavis on 6-minute walk distance?*

A. In the randomized, placebo-controlled, phase 3 clinical trial, the absolute change in 6-minute walk distance measured (using all available data and no imputation) 30 minutes after inhalation among patients with PAH was greater in the iloprost group compared to the placebo group at all time points. At week 12, the placebo-corrected difference was 40 meters ($p < 0.01$). When walk distance was measured immediately prior to inhalation (trough), the improvement compared to placebo was approximately 60% of the effect seen at 30 minutes after inhalation.

Q. *What was the design of the STEP trial?*

A. The STEP trial was a small, randomized, double-blind, placebo-controlled Phase 2 study. The study compared patients with pulmonary arterial hypertension receiving bosentan plus Ventavis ($n=34$) with PAH patients receiving bosentan plus placebo ($n=33$). The mean daily inhaled dose of Ventavis was 27 mcg and the mean number of inhalations per day was 5.6. Patients treated with bosentan tolerated the addition of inhaled Ventavis. Safety trends in patients receiving concomitant bosentan and Ventavis were consistent with those observed in the larger experience of the Phase 3 study (AIR).

Q. *What are the most common adverse reactions with Ventavis?*

A. In clinical studies, common adverse reactions due to Ventavis included: vasodilation (flushing, 27%), cough (39%), headache (30%), flu syndrome (14%), nausea (13%), trismus (12%), hypotension (11%), insomnia (8%), and syncope (8%); other serious adverse events reported with the use of Ventavis included congestive heart failure, chest pain, supraventricular tachycardia, dyspnea, peripheral edema, and kidney failure.

Q. *How can I manage the risk of syncope with Ventavis?*

A. Vital signs should be monitored while initiating Ventavis. In patients with low systemic blood pressure, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mm Hg. Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of syncope. Syncope can also occur in association with pulmonary arterial hypertension, particularly in association with physical exertion. The occurrence of exertional syncope may reflect a therapeutic gap or insufficient efficacy, and the need to adjust dose or change therapy should be considered.

Q. *How many times a day should patients inhale Ventavis, and do they need to take it during sleeping hours?*

A. Ventavis should be taken 6 to 9 times per day (not more than once every 2 hours) during waking hours, according to individual need and tolerability. In the randomized, placebo-controlled, Phase 3 clinical trial, the mean number of inhalations per day was 7.3 and 90% of patients in the iloprost group never inhaled study medication during sleeping hours.

Q. *Why must Ventavis be administered only with the I-neb® AAD® System or the Prodose® AAD® System?*

A. Although there are many aerosolized devices approved in the U.S., it is essential that Ventavis be dosed only via either of two pulmonary drug delivery systems: the I-neb® AAD® System or the Prodose® AAD® System. Only the I-neb and the Prodose have been proven to deliver safe and accurate dosing of Ventavis.

Standard air-jet nebulizers/compressors or ultrasonic nebulizer systems, such as those used to deliver inhalation solutions for asthma, are continuous flow systems that constantly generate aerosol. Patients typically have a 40:60 inhalation:exhalation ratio; therefore, about 60% of the drug is wasted to the environment with such devices during exhalation. Additionally, a variable amount of drug is inhaled by each patient because individual breathing patterns differ (e.g., short, shallow breaths to long, deep breaths). Variable dosing is acceptable for drugs with a broad therapeutic window (e.g., albuterol and ipratropium bromide); however, Ventavis is a potent prostacyclin analogue with a narrow therapeutic index. Precise, reproducible dosing of Ventavis to every patient is critical for the safety and efficacy of the drug.

Q. *What makes the AAD® System unique?*

A. The I-neb and Prodose use Adaptive Aerosol Delivery (AAD®) technology to precisely and reproducibly deliver Ventavis to every patient, at either dose (2.5 mcg or 5.0 mcg), using a single ampule of medication. The AAD® System monitors a patient's unique breathing pattern and adapts to breathing changes during treatment. The I-neb and Prodose deliver Ventavis in the form of a mist only upon inhalation. This is the time when the body can best absorb the medication.

With the Prodose, the dose each patient receives is controlled by a specific dose-control disc that fits into the handpiece of the system. There are separate, clearly marked, and differently colored discs provided for the 2.5 mcg and 5.0 mcg doses.

With the I-neb, a medication chamber controls the dose and a control disc operates the I-neb® AAD® System.

Once a patient receives a complete dose, the I-neb and Prodose stop delivering aerosol and signal the user with visual and audible indicators.

Q. *Why is the volume of Ventavis needed to deliver 2.5 mcg or 5.0 mcg larger than those doses?*

A. The "extra" iloprost solution is required because of incomplete drug transfer from the ampule, the residual volume needed for the AAD® System to produce aerosol, and inefficiencies in drug delivery, such as condensed aerosol clinging to the interior surfaces of the device. Only one drug treatment (either 2.5 mcg or 5.0 mcg) can be delivered from the contents of a single ampule. Reuse of any drug solution that remains after completing a drug treatment, even if the reservoir is "topped off" with fresh medication, will not give accurate dosing. All drug solution remaining in the I-neb or Prodose after a drug

treatment should be discarded and the I-neb or Prodose parts cleaned prior to starting the next treatment.

Q. *What Ventavis aerosol particle size is produced by the I-neb® AAD® System and the Prodose® AAD® System?*

A. Van Dyke and Nikander conducted an *in vitro* study to determine the mass median aerodynamic diameter (MMAD) and fine particle fraction (FPF, % particles < 4.7 μm) of iloprost when delivered via three AAD® systems. The MMADs of the three devices—HaloLite®, Prodose®, and I-neb®—were 1.4 μm , 1.7 μm , and 2.1 μm , respectively. The FPFs for these devices were 91%, 82%, and 82%, respectively. The investigators concluded that all three AAD® systems produce aerosol with a high FPF and low MMAD, both prerequisites for efficient delivery of Ventavis to the pulmonary arterial bed.

Q. *How large are the I-neb and Prodose?*

A. The I-neb is a compact, lightweight, battery-powered system that is approximately 6 inches high and weighs less than 8 ounces. The Prodose is about the size of a two-slice toaster and weighs 7 pounds. It is powered by a standard 110 volt outlet. Each patient is provided with either two I-neb or two Prodose systems. A convenient carrying bag, complete with room for supplies, is provided with each pulmonary drug delivery system.