Medically Led Sessions #5 **9:00 am – 10:00 am**

Endothelin Antagonists (Bosentan [Tracleer], Sitaxsentan [Thelin], Ambrisentan [Letaris]) Grand Ballroom J

Presenters:
David B. Badesch, MD; Univ. of Colorado Health Sciences Center
Deb McCollister, RN; Univ. of Colorado Health Sciences Center
Michael D. McGoon, MD; Mayo Clinic, Minn.
Ivan M. Robbins, MD; Vanderbilt Univ., Tenn.

When should endothelin antagonists be used? What can we expect regarding response and side effects? Now that we have multiple therapies in this class available, how do we choose which to use? Are there important differences among them that patients need to understand? This session will include a broad overview of treatment with endothelin antagonists, including potential benefits and risks.

The following information is extracted from the PHA Website's Fact Sheets on the two ERA's currently approved by the FDA, and is intended to provide general information only. It should not be considered to be medical advice for individual patients, or an endorsement of any specific product. Medical therapy should always be guided by an expert in the field who is familiar with the individual patient's specific situation.

Ambrisentan

What is ambrisentan? Ambrisentan is an oral medication used to treat pulmonary arterial hypertension (PAH). It was approved by the Food and Drug Administration (FDA) in 2007 for the treatment of pulmonary arterial hypertension in patients with New York Heart Association (NYHA) Class II or III symptoms. Ambrisentan is part of a class of medication called endothelin receptor antagonists or ERAs.

How does ambrisentan work? Ambrisentan works by blocking the effects of a substance called endothelin, which is made by the body in increased amounts in patients with PAH. Endothelin causes blood vessels to narrow (constrict). It also causes overgrowth of the muscle in the walls of the blood vessels in the lungs. By blocking the action of endothelin, ambrisentan can reduce blood pressure in the lungs and improve activity level and well being in PAH patients. Studies demonstrate that ambrisentan improves the exercise capacity and delays clinical worsening in PAH patients; long-term trials of the drug showed sustained benefit in exercise capacity.

How is ambrisentan given? Ambrisentan is taken orally. The initial dose for most patients is 5-mg once daily. If there are no problems or side effects after one month, the dose is increased to 10 mg once daily. Both doses are FDA approved.

What are the frequent side effects of ambrisentan? Side effects and precautions taking this medication are typical of other ERA's. The most frequent side effects of ambrisentan were swelling of the lower extremities, nasal congestion, sinusitis, flushing, palpitations, abdominal pain and constipation. The red blood cell count or hematocrit may decrease in some patients but is rarely important. Ambrisentan can interact with Cyclosporine A, a medication given to prevent transplant rejection, anti-fungal medications such as ketoconazole, and acid-reflux medications. The major potential side effect of ambrisentan is damage to the liver. The development of abnormal liver function tests (LFTs), measured in blood samples to greater than three times the upper limit of normal is observed in about 3% of patients receiving this medication. Ambrisentan has been shown to be harmful to the growing fetus in rats. Therefore, pregnancy should be avoided in women treated with ambrisentan. There is also concern that ambrisentan can effect the development of human sperm. It is not known whether ambrisentan is excreted in human milk, though studies show that it is passed through breastfeeding in rats. Therefore, nursing mothers should not take ambrisentan.

Monitoring for side effects of ambrisentan: Because of the potential for damage to the liver, liver function tests must be obtained on a monthly basis as long as a patient is receiving ambrisentan. Because of the potential harm to the fetus, women of childbearing potential must also have a monthly pregnancy test. Hematocrit (blood count) should

be monitored once a month.

Pregnant and nursing women Use of ambrisentan is contraindicated in pregnancy. If a patient becomes pregnant while taking ambrisentan, she should immediately notify the prescribing physician. It is not known whether ambrisentan passes into breast milk.

Use in children The safety and effectiveness of ambrisentan has not been studied in children.

Bosentan

What is bosentan? Bosentan is an oral medication used to treat pulmonary arterial hypertension (PAH). It was approved by the Food and Drug Administration (FDA) in 2001 for the treatment of pulmonary arterial hypertension in patients with New York Heart Association (NYHA) Class III or IV symptoms. Bosentan is part of a class of medications called endothelin receptor antagonists or ERAs.

How does bosentan work? Bosentan works by blocking the effects of a substance called endothelin, which is made by the body in increased amounts in patients with PAH. Endothelin causes blood vessels to narrow (constrict). It also causes scarring and overgrowth of the muscle in the walls of the blood vessels in the lungs. By blocking the action of endothelin, bosentan can lead to a reduction in the blood pressure in the lungs and to improvement in activity level and wellbeing. While improved exercise capacity and increased sense of wellbeing have been demonstrated in short-term studies of Tracleer, there is less information regarding long-term effects. A recent study suggested that it may improve survival in NYHA class III patients.

How is bosentan given? Bosentan is a pill that is taken orally twice a day. The initial dose for most patients is 62.5 mg twice a day. If there are no problems or side effects after one month, the dose is increased to 125 mg twice a day, which is the FDA approved dose.

What are the frequent side effects of bosentan? Reported side effects include nasal congestion, headache, flushing, and lower extremity swelling. The red blood cell count or hematocrit may decrease in some patients but is rarely important. Bosentan can interact with cholesterol reducing medications, decreasing their effectiveness. The major potential side effect of bosentan is damage to the liver. in The development of abnormal liver function tests (LFTs), measured in blood samples to greater than 3 times the upper limit of normal is observed in about 10% of patients receiving this medication. However, bosentan has been given to thousands of patients without any reports of permanent liver damage. Bosentan may decrease the effectiveness of hormonal contraceptives given by any route. Hormonal contraceptives should not be used alone for the prevention of pregnancy during treatment with bosentan. Bosentan has been shown to be harmful to the growing fetus in rats. Therefore, pregnancy should be avoided in women treated with bosentan Bosentan may lower sperm counts and decrease the ability to father children; this may be irreversible.

Monitoring for side effects of bosentan: Because of the potential for damage to the liver, liver function tests must be obtained on a monthly basis as long as a patient is receiving bosentan. Because of the potential harm to the fetus, women of childbearing potential must also have a monthly pregnancy test. Hematocrit (blood count) should be monitored at least once every three months. In patients receiving cholesterol lowering medications, cholesterol levels should also be checked at the end of the first month of therapy, as well as every six months, to determine if dosing should be adjusted.

Do not take bosentan if:

- You are pregnant, plan to become pregnant, or become pregnant during treatment with bosentan. Notify your treating physician immediately if you become pregnant while receiving bosentan.
- Your blood tests show possible liver injury before starting therapy.
- You are taking cyclosporine-A, glyburide or ketaconazole.

Pregnant and nursing women Use of bosentan is contraindicated in pregnancy. If a patient becomes pregnant while taking bosentan, she should immediately notify the prescribing physician. It is not known whether bosentan passes into breast milk

Use in children Bosentan has been studied in children and appears to be safe. However, the dose may need to be adjusted and should be discussed with the prescribing physician.