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Abstract

Objective: The purpose of this study to examine the efficacy and safety doses of ambrisentan in patient with pulmonary arterial hypertension. **Background:** Pulmonary arterial hypertension is a life threatening and progressive diseases with limited treatment option. Endothelin is a vasoconstrictor and smooth muscle cell mitogen (that plays critical role in the pathogens and progression of PAH. **Methods:** In this regard the writer uses different methods collection of data from different sources. The writer uses books, journal, internet, company visits (RENETA) for IMS data. **Result:** There are five drugs available in the international market for the treatment of PAH. By comprising all the drugs it is found that Ambrisentan is better than all others. **Conclusion:** Ambrisentan appears to improve exercise capacity, symptom, and hem dynamics in patients with pulmonary arterial hypertension .The incidence and severity of liver enzyme abnormalities appears to low.

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I. Background:

1. Pulmonary Arterial Hypertension

1.1 Introduction:

Pulmonary arterial hypertension (PAH) is a chronic, progressive disease characterized by increased pulmonary vascular resistance of the lung microvasculature, intimal hyperplasia and smooth muscle cell hypertrophy, and thrombosis (Rubin LJ 2006). PAH disease progression leads to right heart failure and death (Vlahakes GJ, Turley K, Hoffman JI. 1981; D'Alonzo GE, Barst RJ and Ayres SM 1991, Rich S 2001).

PAH is defined by mean pulmonary arterial pressure that exceeds 25 mm Hg at rest or 30 mm Hg during exercise, with mean pulmonary-capillary wedge pressure or left ventricular end diastolic pressure ≤15 mm Hg and pulmonary vascular resistance greater than 3 Wood units. A wood unit means that non standard unit for expressing pulmonary vascular resistance (mmHg/L) One wood means is -80 dyn.cm.sec. (Hatano S, StrasserT 1975; Barst RJ, McGoon M and Torbicki A 2004b). Unfortunately and despite significant efforts to diagnose patients earlier in the disease process, the disease is most often diagnosed months or years after symptoms first appear. As a consequence, the majority of patients present with advanced disease and marked functional impairment (Hoeper 2005).

1.2 Clinical classification of pulmonary arterial hypertension:

According to the Venice 2003 World Health Organization (WHO) symposium on PAH classification, the broader category of pulmonary hypertension (PH) is subdivided into 5 categories based on association with heart disease, lung disease, thromboembolic disease or miscellaneous conditions (Table) (Simonneau G, Galie N, Rubin LJ et al 2004). PAH can occur in the absence of an associated disorder as either idiopathic PAH (IPAH) or familial PAH (FPAH) (Rubin LJ et al 2005a). Additionally PAH can occur as a complication of systemic conditions, such as connective tissue disease, congenital heart disease, portal hypertension, HIV infection, or from the use of anorexigens, amphetamines, or cocaine (Rubin LJ et al 2005a).

Table-1: **Clinical classification of pulmonary hypertension (Venice 2003).**

1. Pulmonary arterial hypertension (PAH)

1.1 Idiopathic (IPAH)

1.2 Familial (FPAH)

1.3 Associated with (APAH):

1.3.1 Collagen vascular disease

1.3.2 Congenital systemic-to-pulmonary shunts

1.3.3 Portal hypertension

1.3.4 HIV infection

1.3.5 Drugs and toxins

1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)

1.4 Associated with significant venous or capillary involvement

1.4.1 Pulmonary veno-occlusive disease (PVOD)

1.4.2 Pulmonary capillary hemangiomatosis (PCH)

1.5 Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension with left heart disease

2.1 Left-sided atrial or ventricular heart disease

2.2 Left-sided valvular heart disease

3. Pulmonary hypertension associated with lung diseases and/or hypoxemia

3.1 Chronic obstructive pulmonary disease

3.2 Interstitial lung disease

3.3 Sleep-disordered breathing

3.4 Alveolar hypoventilation disorders

3.5 Chronic exposure to high altitude

3.6 Developmental abnormalities

4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease

4.1 Thromboembolic obstruction of proximal pulmonary arteries

4.2 Thromboembolic obstruction of distal pulmonary arteries

4.3 Non-thromboembolic pulmonary embolism (tumor, parasites, foreign material)

5. Miscellaneous

Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

One to two persons per million per year are diagnosed with either IPAH or FPAH (Abenhaim L, Moride Y, and Brenot F 1996), with at least 6% of these patients having FPAH (Rich et al 1987). However, IPAH comprises the minority of PAH cases, and the incidence of PAH associated with other conditions is generally higher than that for IPAH/FPAH. Histologic features consistent with PAH and clinically evident pulmonary hypertension have been observed in connective tissue diseases including scleroderma, systemic lupus erythematosus, mixed connective tissue disease, polymyositis, dermatomyositis, and rheumatoid arthritis (Rich et al 2001; Farber HW, Loscalzo J 2004). Estimates for PAH in scleroderma patients vary widely from 11% to 35%, representing an incidence of 50 to 230 cases per million (Rich et al 2001).

1.3 Causes of Pulmonary Arterial Hypertension:

Pulmonary hypertension (PH) is the result of a process that begins with changes in the cells that line our lungs' arteries. This process includes three types of changes that affect the pulmonary arteries:

- The walls of the arteries tighten.
- The walls of the arteries are stiff at birth or become stiff from an overgrowth of cells.
- Blood clots form in the arteries.

These changes make it hard for the heart to push blood through the arteries and into the lungs. Thus, the pressure in the arteries rises, resulting in PH. (Beghetti M 2006)
But the exact cause of pulmonary arterial hypertension remains unknown. However, continuous researches, researchers discovered a certain factor appear to increase or developing pulmonary arterial hypertension (PAH). They include:

- Use of appetite suppressants, especially fenfluramine (fen-FLOO-ra-men) and dexfenfluramine (deks-fen-FLOO-ra-men)
- Chronic use of cocaine or amphetamines
- HIV infection
- Liver disease
- Connective tissue diseases, such as scleroderma or lupus. (MacGreggor AJ, Canavan R, Knight C2001; Galie N, Manes A and Branzi A 2003)

1.4 Signs and Symptoms of Pulmonary Arterial Hypertension:

Difficulty breathing or shortness of breath (dyspnea) is the main symptom of pulmonary arterial hypertension (PAH).Other common symptoms and sign are availavle.Such as

- Fatigue
- Dizziness
- Fainting spells (syncope)
- Swelling in the ankles or legs (oedema)
- Bluish lips and skin (cyanosis)
- Chest pain
- Racing pulse
- Palpitations (a strong feeling of a fast heartbeat).(Gibbs J and Higgenbottam T 2001)

1.5 Treatment of Pulmonary Arterial Hypertension:

There is currently no cure for pulmonary arterial hypertension but advances in understanding about how the disease develops mean that licensed treatments have become are available which have helped to improve prognosis and quality of life for patients with this disease. Treatment options for patients with Pulmonary Arterial Hypertension fall into two main areas: general therapies that are used to reduce symptoms but which do not have a positive impact on the disease progression, and disease-targeted therapies that have been specifically researched in the area of Pulmonary Arterial Hypertension (PAH).(Nazzareno G, Seeger W and Naeije R 2004)

1.5.1 General treatments:

1.5.1.1 Anticoagulants:

Anticoagulant is substance which is used to prevent coagulation (coagulation means that is a complex process by which blood from clots. It is part of hemostasis) and that stop blood clots from forming in the lungs. Example:Warfarin.(www.rxlist.com)

1.5.1.2 Diuretics:

Diuretics is drugs which reduce the rate of urination that means of forced diuresis(increased urine formation by diuretics and fluid). Example:Hydrochlorothiazide(www.rxlist.com)

1.5.1.3 Calcium channel blockers:

Relax blood vessels and increase the supply of blood and oxygen to the heart, while reducing its workload. These drugs can be very helpful, but only for a small amount of patients. All patients that take them should be monitored carefully. Example:Verapamil,Gallopamil (Goodman and Gilman,s- Page:1028.)

1.5.1.4 Epoprostenol:

Epoprostenol is an intravenous medication that used to treat PAH. It is a synthetic form of a substance that made by the body called prostacycline,Epoprostonol dilates blood vessels, prevent the smooth muscle cell in there walls from contracting and reduced the stickiness of circulating platelets which might otherwise sludge up the vessels. It also help right side of the heart to better pump blood through through the lungs. (Goodman and Gilman,s- Page: 1028).

1.5.1.5 Treprostinil:

Treprostinil is another prostacyclin, also relaxes blood vessels and increases the supply of blood to the lungs, reducing the workload of the heart. It can be given under the skin. (Goodman and Gilman,s-page -1030)

1.5.1.6 Bosentan:

Bosentan is oral medication that used treatment of PAH. (www.rxlist.com)

1.5.1.7 Nitric oxide inhalation:

Nitric oxide inhalation which causes the pulmonary arteries to widen or open is also being used by some doctors. (www.rxlist.com)

1.5.1.8 Sildenafil:

Sidenafil is another drug that causes the pulmonary arteries to open, has recently been shown to improve the condition of PAH patients. This drug is available in pill form. (www.rxlist.com)

1.5.1.9 Diuretics (water or fluid pills):

Diuretics help ease symptoms and improve the heart's performance in some patients with PAH. (www.rxlist.com)

1.5.1.10 Oxygen:

May need oxygen therapy if the level of oxygen in our blood is low. Oxygen is usually given through nasal prongs or a mask. Over time, may need oxygen around the clock. (www.mediafact.com)

1.5.2 Lung transplantation:

Surgery to replace one or both diseased lungs with healthy lungs from a human donor may help some patients. This procedure is usually recommended for patients for whom medical therapy is no longer effective. Complications include rejection by the body of the transplanted lung and infection. Transplant patients must take medicines for life to reduce the chances that their body will reject the transplanted lung. (www.rxlist.com)

1.5.3 Other Possible Treatments

Researchers also are studying whether stem cell transplantation combined with gene therapy may provide a cure for PAH in the not too distant future. (www.mediafact.com)

II. Drug Description

2. Ambrisentan:

Ambrisentan is a vasodilator drug. That has been used for the treatment of Pulmonary Arterial Hypertension (PAH). Ambrisentan is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist that is selective for the endothelin type-A (ETA) receptor. (www.pubmedcentral.nih.gov)

2.1 Chemical composition of Ambrisentan:

The chemical name of Ambrisentan is (+)-(2S)-2-[(4, 6-dimethylpyrimidin-2-yl) oxy]-3-methoxy-3, 3-diphenylpropanoic acid. It has a molecular formula of C22H22N2O4. And it's molecular weight of 378.42. It contains a single chiral center determined to be the (S) configuration.

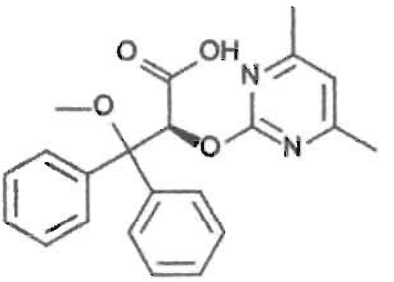


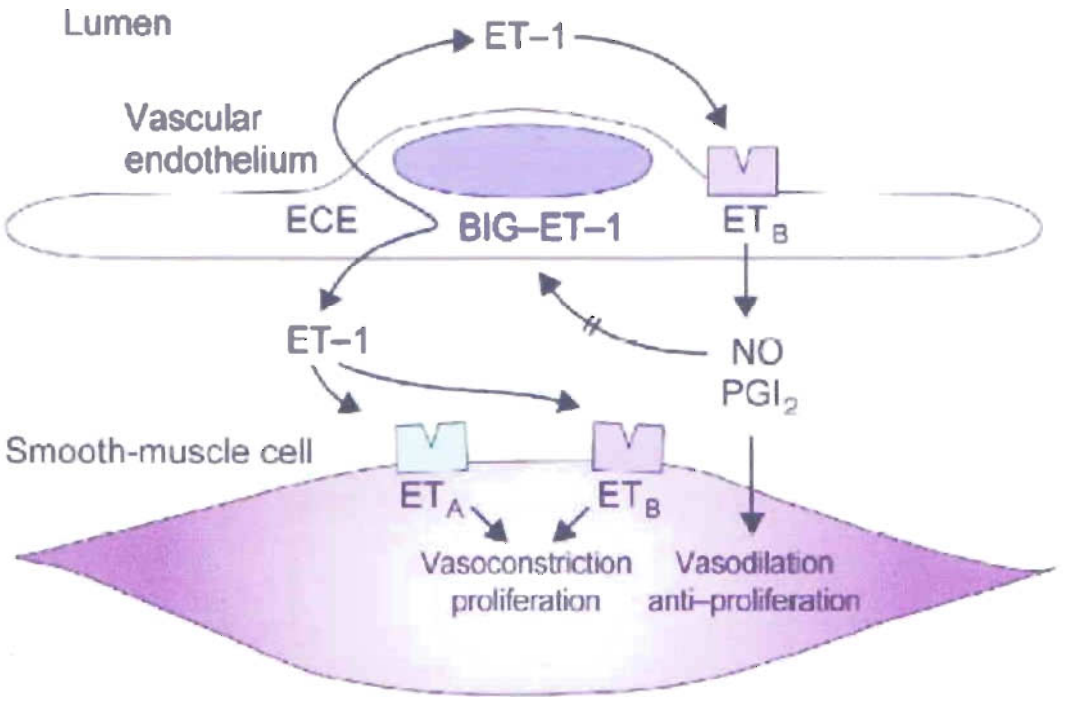
Figure 1 - Ambrisentan Structural Formula

Ambrisentan is a white to off-white, crystalline solid. It is a carboxylic acid with a pKa of 4.0. It is also practically insoluble in water and in aqueous solutions at low pH. Solubility increases in aqueous solutions at higher pH. In the solid state Ambrisentan is very stable, is not hygroscopic, and is not light sensitive. (www.mediafact.com).

2.2 Mechanism of Action:

Ambrisentan is an endothelin receptor antagonist drug that blocks the action of endothelin, a very potent naturally occurring vasoconstrictor and proliferation that is capable of causing severe narrowing of the blood vessels. There are two types of endothelin receptors: ETA and ETB. (Dupuis J 2001.)

When endothelin binds with ETA receptors, it causes the narrowing of the blood vessels (vasoconstriction). When endothelin binds with ETB receptors, it produces nitric oxide and prostacyclin, relaxing and widening the blood vessels (vasodilation). The ETB receptors exist to counteract the ETA receptors and prevent against excessive narrowing of the blood vessels (Alie N, Manes A, Branzi A. Res; 2004; Hirata Y, Emori T and Eguchi S 1993.)



Mechanism action of Ambrisentan.

2.3 Pharmacokinetics:

The absolute bioavailability of ambrisentan is not known. Ambrisentan is rapidly absorbed with peak concentrations occurring approximately 2 hours after oral administration in PAH patients. Food does not affect it bioavailability. Ambrisentan is highly bound to plasma proteins (99%), (Rubin LJ et al 2005).

The elimination of ambrisentan is predominantly by non-renal pathways, but the relative contributions of metabolism and biliary elimination have not been well Although ambrisentan has a 15-hour terminal half-life, the mean trough concentration of ambrisentan at steady-state is about 15% of the mean peak concentration and the accumulation factor is about 1.2 after long-term daily dosing, indicating that the effective half-life of ambrisentan is about 9 hours. (Oudiz R, Torres F and Frost A 2006).

2.4 Safety:

Ambrisentan is generally safe and well tolerated in all the PAH. The most frequently reported adverse events during the Phase 2, dose-ranging study were peripheral edema, nasal congestion, upper respiratory tract infection, headache, flushing, and nausea and did not appear to be dose related.(Galie N, Badesch D and Oudiz R 2005).
Ambrisentan was well tolerated throughout the 1-year extension study, with no emergent safety signals apparent during long-term therapy. (Galie N, Keogh AM and Frost A 2005).

2.5 Clinical Efficacy:

The main efficacy endpoint tested in trials of ambrisentan is improvement in 6 minute walk distance. With doses of 1 mg, 2.5 mg, 5 mg and 10 mg 6 MWD improved Significantly at 12 weeks. (Gerber MJ, Dufton C and Pentikis H 2006). Whilst data for the PAH subgroup were suggestive of a dose-response relationship, the overall data did not support this conclusion. The twenty-four week data from the study extension showed a better 6 MWD response for the PAH group compared with the other causes of PAH (64.3 compared with 38.5 m, p 0.05 two-sample-test). (Barst et al 2006a). ARIES showed a placebo-corrected increase in 6 MWD in each dose group at week 12 compared with placebo of; 31 m (p □0.008) and 59 m (p 0.001)or 5 and 10 mg respectively in ARIES-1, 32 m and59 m for 2.5 mg and 5 mg respectively in ARIES-2(p □ 0.001).43 6 MWD in the combined 5 mg dose group improved by 45 m with a p-value of 0.001.Integrated data from 383 patients on ambrisentan mono therapy showed that improvement in 6 MWD had been maintained at 48 weeks (36 m) from 38 mat twelve weeks. (Oudiz R et al 2006).Time to clinical worsening was shown to be longer with ambrisentan (log-rank test, p □0.005) in the Ambrisentan in PAH combined 5 mg dose group and in ARIES-2 at both the2.5 and 5 mg (p □ 0.01) doses, but not in ARIES-1 In both ARIES trials clinical worsening was defined by the combined end points of death, lung transplantation, hospitalization for PAH, atria septostomy, study withdrawal due to escape criteria or study withdrawal due to the addition of other PAH therapeutic agents. (Galie N and Badesch D 2005a). The extended ARIES-E data reports an event free survival of 79.2% for CTD-PAH and 85.5% for PAH after one year. In the clinical trial worsening criteria included an increase in the patient's diuretic requirement. Of the thirteen and eight patients reported to have deteriorated from0–12 and 12–24 weeks respectively, eleven of them were due to increases in diuretic therapy. Survival at 12 weeks in patients treated with ambrisentan in clinical trials was 97%, 99% and 98% in the 2005study, ARIES-1 and ARIES-2 respectively. In the week extension of the ARIES trials survival was95 (Kenyon kw, Nappi JM 2003a). The ARIES-E data in abstract form reported al year estimated survival of 90.3% in the 124 enrolled CTD-PAH patients.51Borg dyspnea scores at 12 weeks compared with placebo improved significantly for the 10 mg dose and the combined 5 mg and 10 mg data in ARIES-1 and the 2.5 mg and 5 mg doses separately and combined in ARIES-2 and the combined 5 mg Dose group. (Gerber kJ, Dufton C and Pentikis H 2006) In the earlier study improvements seen in Borg dyspnea index at 12

weeks were maintained at 24 weeks in all doses In ARIES-1 the number of subjects whose functional class deteriorated at 12 weeks was less with ambrisentan than placebo resulting in a significant improvement in functional class distribution. A similar trend seen in ARIES-2 was not significant, but the combined 5 mg data also showed significant Improvement. In study the functional class improvement seen in a few patients at 12 weeks was maintained to 24 weeks. BNP data from 110 patients in ARIES-1 showed both the 5 mg and 10 mg dose reduced BNP levels compared with placebo (0.005 and 0.001). In ARIES-2 a similar effect was seen (0.005 for both 2.5 mg and 5 mg dose); data from 107 patients was available. The ARIES trials did not include repeat assessment of hemodynamic variables. Of the 64 patients in the dose-ranging study there is only follow up right heart catheter data for 29 patients. Ambrisentan would appear to produce a good hemodynamic response with a significant fall in m PAP and PVR. This is comparable to other ERA therapies in trials although the lack of corroborative data and the small number of patients suggest further work would be beneficial.

2.6 Drug–drug interactions:

Now days sulfonamide-class ERAs developed for the treatment of PAH are associated with potentially significant drug-drug interactions. So as result Bosentan induces the cytochrome P450 isoenzymes CYP2C9 and CYP3A4 and may decrease the systemic exposure of other drugs (Kenyon kw and Nappi JM 2003). Similarly, remodulin inhibits the activity of CYP2C9, thereby increasing systemic exposure to drugs metabolized by this cytochrome P450 isozyme (Barst RJ, Langleben D and Frost A 2004). Both bosentan and Remodulin alter the pharmacokinetics of warfarin (Kenyon et al 2003; Badesch DB, Abman SH, Ahearn GS 2004a; Dingemanse J, van Giersbergen PL 2004; Barst RJ, Langleben D and Badesch D 2006). While the effects of concomitant bosentan may or may not require adjustment of warfarin dose, an 80% reduction in the dose of warfarin was used i to prevent over-anticoagulation and the potential for bleeding (Barst et al 2006). Additional drugs commonly prescribed to patients with PAH that are metabolized by the cytochrome P450 system include sildenafil, hormonal contraceptives, glyburide, cyclosporin A, and statins.

Potential drug–drug interactions between ambrisentan and sildenafil, and between ambrisentan and warfarin were evaluated in healthy subjects co-administered ambrisentan plus sildenafil or ambrisentan plus warfarin, respectively. Pharmacokinetic parameters of ambrisentan and sildenafil were similar when administered as monotherapy or in combination (Dufton C, Gerber MJ and Yin O 2006). The pharmacokinetics of n-desmethyl-sildenafil, the active metabolite of sildenafil, were also unaffected by multiple doses of ambrisentan (Dufton et al 2006). Similarly, the pharmacokinetics of warfarin enantiomers and ambrisentan were not appreciably influenced by concomitant administration (Gerber MJ, Dufton C and Pentikis H 2006). Moreover, co-administration of multiple ambrisentan doses had no clinically relevant effect on the prothrombin time or international normalized ratio following a single dose of warfarin (Gerber et al 2006). In both studies, ambrisentan is well tolerated and no safety concerns arose with the combination therapies.

The lack of pharmacodynamic effect of ambrisentan on warfarin has been confirmed in ambrisentan clinical trials to date, which allowed the use of warfarin or warfarin-like anticoagulants as concomitant medications. In a Phase 2, dose-ranging study,

prothrombin time, international normalized ratio, and anticoagulant dose were unaffected by ambrisentan treatment (Galie N, Badesch D and Oudiz R 2005a). Similar results were reported for warfarin-type anticoagulant dosing in the Phase 3 ambrisentan trials (Olschewski H, Galie N, Ghofrani HA 2006; Oudiz R, Torres F and Frost A 2006). These data suggest that dosage adjustment of warfarin is not needed during concomitant ambrisentan therapy.

2.7 Clinical Particulars:

2.7.1 Therapeutic indication

Ambrisentan is indicate for the treatment of pulmonary arterial hypertension in patients (WHO Group 1) And also WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. Ambrisentan prevents thickening of the blood vessels especially those in the lungs and heart. It helping patient's heart pump blood more efficiently. It improves ability to exercise and prevents patient's condition from getting worse. (Oudiz R et al 2006)

2.7.2 Posology and method of administration:

Ambrisentan is to be taken orally at a dose of 5 mg once daily. It is recommended that the tablet is swallowed whole and it can be taken with or without food. (Tuder RM, Cool CD and Geraci MW 1999)

Some additional efficacy has been observed with 10 mg ambrisentan in patients with class III symptoms, however an increase in peripheral oedema has also been observed. Patients with PAH associated with connective tissue disease may require 10 mg ambrisentan for optimal efficacy. Confirm that the 5 mg dose is well tolerated before considering an increase in dose to 10 mg ambrisentan in these patients. Limited data suggest that the abrupt discontinuation of Letairis is not associated with rebound worsening of PAH. (Baumhakel M, Cremers B and Bohm M 2005).

2.7.3 Children and adolescents:

Ambrisentan is not recommended for use in patients below 18 years of age due to a lack of data on safety and efficacy. (Badesch DB, Tapson VF and McGoon MD2000).

2.7.4 Elderly:

No dose adjustment is required in patients over the age of 65. (Badesch DB et al 2000)

2.7.5 Patients with renal impairment:

No dose adjustment is required in patients with renal impairment. There is limited experience with ambrisentan in individuals with severe renal impairment, initiate therapy cautiously in this subgroup and take particular care if the dose is increased to 10 mg Ambrisentan.(McGoon M, Frost A and Oudiz R et al 2006)

2.7.6 Patients with hepatic impairment:

Ambrisentan has not been studied in individuals with severe hepatic impairment. Since the main routes of metabolism of ambrisentan are glucuronidation and oxidation with subsequent elimination in the bile, hepatic impairment would be expected to increase exposure to ambrisentan. Therefore ambrisentan should not be initiated in patients with severeHepatic impairment or clinically significant elevated hepatic aminotransferases. (Rich S, Dantzker DR and Ayres SM 2001)

2.7.7 Dosage forms and strengths:

Letairis is available as 5 mg and 10 mg film-coated tablets. Ambrisentan tablets should be stored at 25°C (77°F), with excursions permitted between 15° and 30°C (59° and 86°F). (www.rxlist.com)

2.7.8 Contraindications:

- Hypersensitivity to the active substance or to any of the excipients
- Pregnancy X (may cause fetal harm when administered to a pregnant woman because there were abnormalities of the lower jaw and hard and soft palate, malformation of the heart and great vessels, and failure of formation of the thymus and thyroid)
- Women of child-bearing potential who are not using reliable contraception
- Lactation
- Severe hepatic impairment (Galie N et al. 2005)

2.7.9 Special warnings and precautions for use:

2.7.9.1 Liver function:

Liver function abnormalities have been associated with PAH. Hepatic enzyme elevations potentially related to therapy have been observed with endothelin receptor antagonists (ERA) .Therefore hepatic aminotransferases should be evaluated prior to initiation of ambrisentan. Ambrisentan treatment should not be initiated in patients with baseline values of ALT and/or AST>3xULN

Monthly monitoring of ALT and AST is recommended. If patients develop sustained, unexplained, clinically significant ALT and/or AST elevation, or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g. jaundice) ambrisentan therapy should be discontinued.

In patients without clinical symptoms of hepatic injury or of jaundice, re-initiation of ambrisentan may be considered following resolution of hepatic enzyme abnormalities. The advice of a hepatologist is recommended. (www.mediafact.com)

2.7.9.2 Haemoglobin concentration

Reductions in haemoglobin concentrations and haematocrit have been associated with ERA including ambrisentan. Most of these decreases were detected during the first 4 weeks of treatment and haemoglobin generally stabilized thereafter.
Initiation of ambrisentan is not recommended for patients with clinically significant anaemia. It is recommended that haemoglobin and haematocrit levels are measured during treatment with ambrisentan for example at 1 month, 3 months and periodically thereafter in line with clinical practice. If a clinically significant decrease in haemoglobin or haematocrit is observed, and other causes have been excluded, dose reduction or discontinuation of treatment should be considered. (www.pah-info.com)

2.7.9.3 Fluid retention

Peripheral oedema has been observed with ERA including ambrisentan. Most cases of peripheral oedema in clinical studies with ambrisentan were mild to moderate in severity, although it appeared to occur with greater frequency and severity in patient's ≥65 years. Peripheral oedema was reported more frequently with 10 mg Ambrisentan.

Post-marketing reports of fluid retention occurring within weeks after starting ambrisentan have been received and, in some cases, have required intervention with a diuretic or hospitalization for fluid management or decompensate heart failure. If patients have pre-existing fluid overload, this should be managed as clinically appropriate prior to starting ambrisentan.

If clinically significant fluid retention develops during therapy with ambrisentan, with or without associated weight gain, further evaluation should be undertaken to determine the cause, such as ambrisentan or underlying heart failure, and the possible need for specific treatment or discontinuation of ambrisentan therapy.
Women of child-bearing potential

Ambrisentan treatment must not be initiated in women of child-bearing potential unless the result of a pre-treatment pregnancy test is negative and reliable contraception is practiced. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynaecologist should be considered. Monthly pregnancy tests during treatment with Ambrisentan are recommended. (www.pah-info.com)

III. Methodology:

The writer used different methods for this work as direct visit to the Pharmaceutical Company (RENETA Pharmaceutical Ltd.). observation of the International Marketing Statistic (IMS) data. The writer also gathered information from books, journal, magazines and internet.

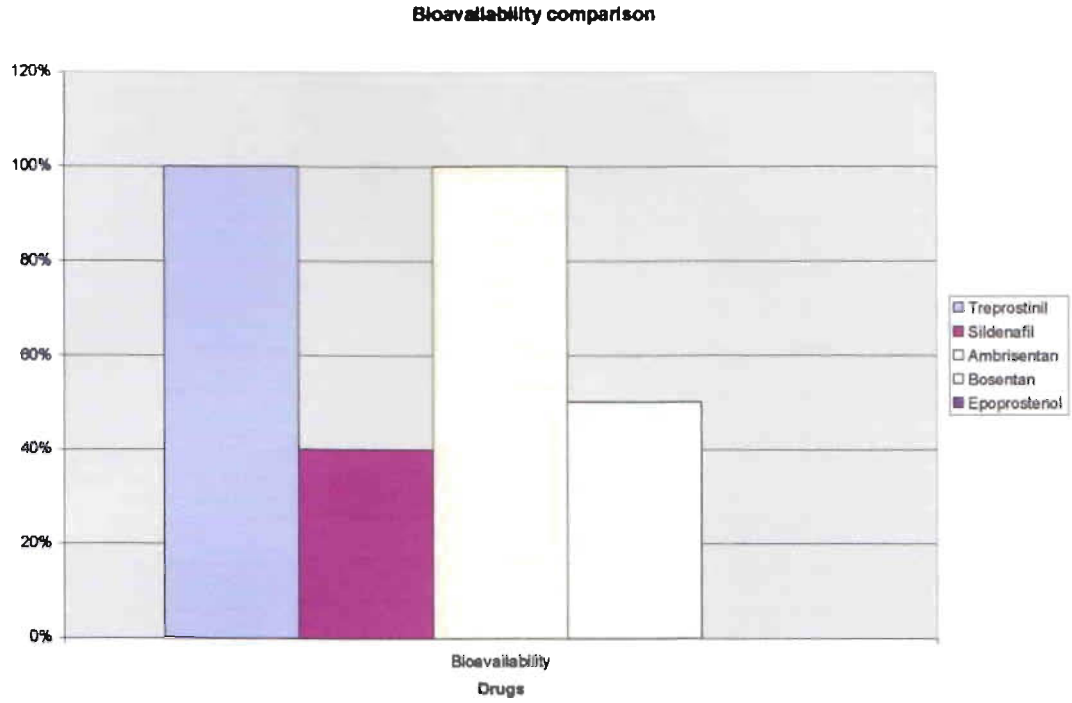
IV. Result & Discussion:

There are many patients of Pulmonary Arterial Hypertension (PAH) in Bangladesh, but there is no direct drug for the treatment of this disease in the country. In the international world market there are five principal drugs for PAH. These are Ambrisentan, Bosentan, Epoprostenol, Treprostinil and Sildenafil. Among them Ambrisentan is better than all other. Following are the data support the claim.

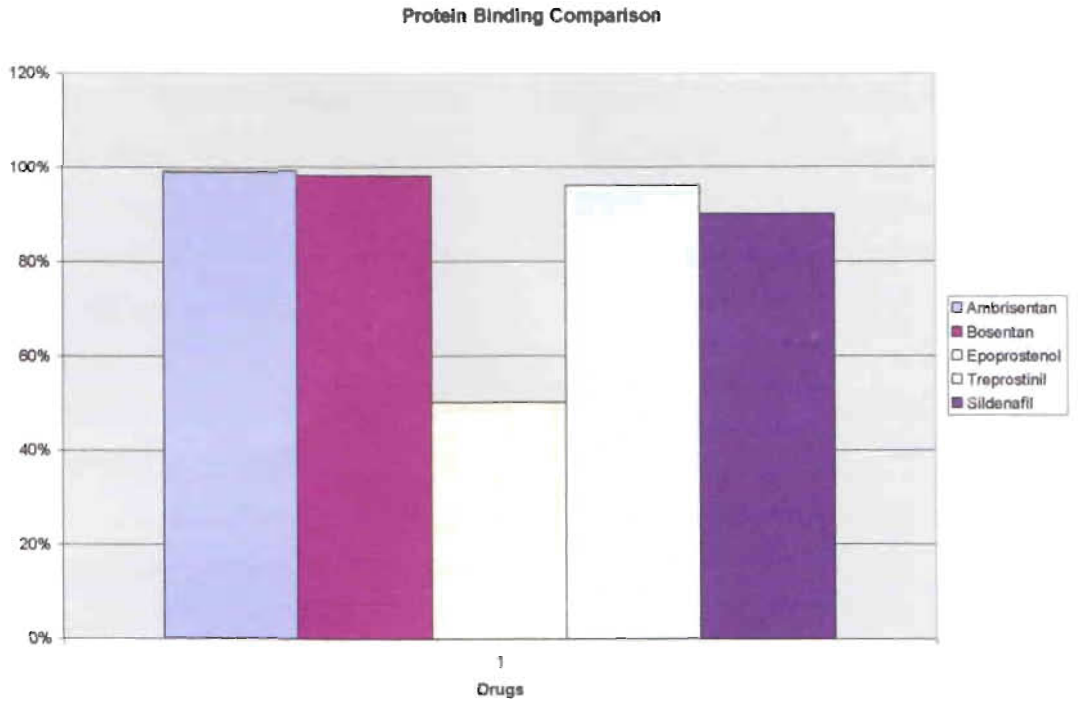
Table-2: Comparison of different drugs:

Drugs	Bioavailability	Half life	Protein binding	Dose	C max
Ambrisentan	100%	15 hours (terminal)	99%	5 and 10 mg	4 to 5 hours after oral dosing
Bosentan	50%	5 hours	>98%	62.5 or125 mg twice daily	3 to 5 hours after oral dosing
Epoprostenol	Undetermined	Undetermined	50%	20 mg	Undetermined
Treprostinil	100%	4 hours	96%	20 mL vials	1.25 to 125 ng/kg/min
Sildenafil	40%	3 to 4 hours	90%	20 mg tablet three times a day	1 hour after oral administration.

Graph-1: Bioavailability comparison:



Graph-2: Protein Binding:



4.1 Comparison between Ambrisentan and Bosentan: Although Both Ambrisentan and Bosentan act on the same receptor, having the same route of administration, both cannot be given in pregnancy and also show hypersensitivity but Ambrisentan is better than Bosentan. Here are the few data that prove the claim.

1. WHO recommended ambrisentan used as functional class II or III and Bosentan used as functional class II or IV. (Rich S,et al 1998.)
2. Improved exercise capacity and cardiopulmonary hemodynamics and was well tolerated at a dose of 125 mg twice daily. (Channick RN, Simonneau G and Sitbon O 2001)

3. Starting dose 5mg and 10 mg but Maintenance dose 5 or 10 mg and Bosentan starting dose 62.5 mg twice daily but maintenance dose 125 mg twice daily for 12 weeks. (Rich S et al 1998.)

4. Ambrisentan has high protein binding (99%) and Bosentan have 98%.ambrisentan have half life 15 hours but Bosentan have 5 hours. (Weber C, Schmitt R and Birnboeck H 1996)

5. Bosentan administered orally reaches peak concentration within 3 to 5 hours and steady state by 3–5 days(Dingemanse J, Bodin F and Weidekamm E 2002).Concomitant administration of bosentan and inhibitors of CYP3A4 can increase the peak plasma concentration by more than 2-fold van (Giersbergen PL, Halabi A, Dingemanse J 2002). Oral ambrisentan reaches peak concentration within 2 hours after administration (Wu C, Decker ER and Blok N 2004a).

6 .The elimination of Bosentan is primarily through the biliary system with only 3% or less excreted through the kidneys (Weber C, Schmitt R and Birnboeck H 1996a). The elimination of ambrisentan is mainly by nonrenal pathways and the relative contributions of metabolism and biliary elimination have not been characterized.

7. Bosentan is extensively metabolized by the liver (Weber et al 1996b). Ambrisentan is a strong inhibitor of P-glycoprotein, organic anion transport protein, cytochrome P450 and uridine 5 diphosphate glucuronosyltransferases UGTs.

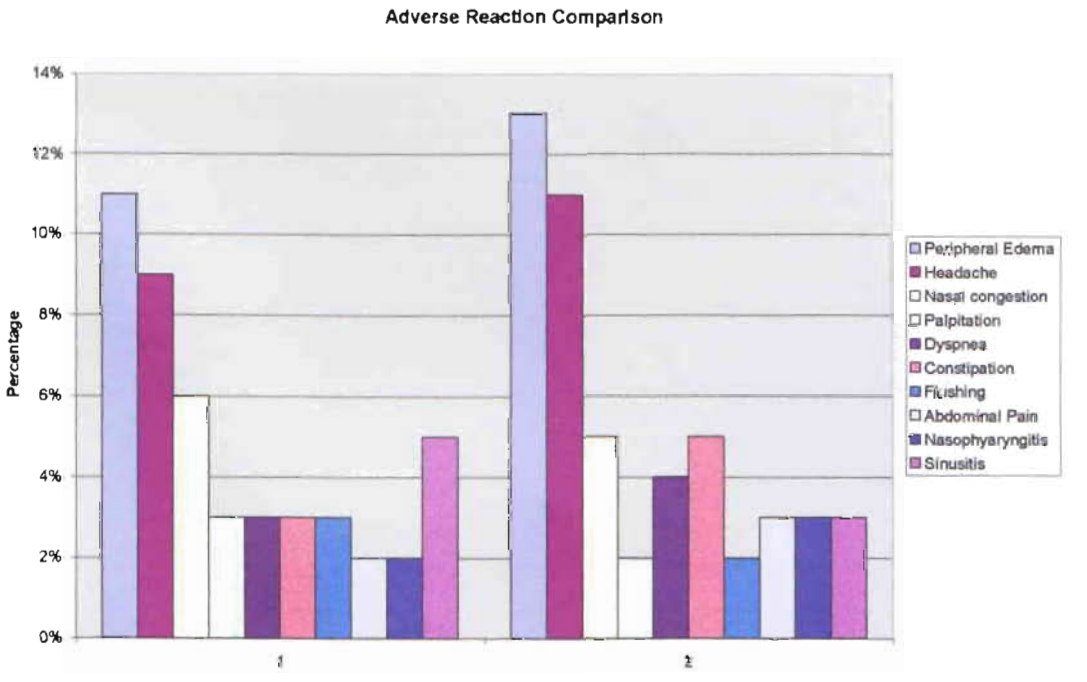
4.2 Adverse reactions

The most frequently reported adverse reactions included peripheral edema, nasal congestion, sinusitis, flushing, palpitations, abdominal pain, and constipation. Adverse reactions occurring in at least 3% of patients treated with ambrisentan and more frequently than with others PAH drugs and that are summarized in Table.
The majority of the adverse reactions were classified as mild to moderate in severity and only the incidence of nasal congestion was dose dependent.(Jacobs A, Preston IR, Gomberg-Maitland M;2006.)

Table-3: Adverse reactions of Ambrisentan and other PAH drugs:

Adverse Reaction	Ambrisentan	Other PAH drugs
Peripheral Edema	11%	13%
Headache	9%	11%
Nasal congestion	6%	5%
Palpitation	3%	2%
Dyspnea	3%	4%
Constipation	3%	5%
Flushing	3%	2%
Abdominal Pain	2%	3%
Nasophyaryngitis	2%	3%
Sinusitis	5%	3%

Graph-1: Adverse reactions of Ambrisentan and other PAH drugs.



Conclusions:

Ambrisentan is a selective ETA receptor antagonist that appears to provide significant clinical benefit in the treatment of patients with PAH. In Phase 2 and 3 clinical trials, ambrisentan improved exercise capacity, dyspnea, and time to clinical worsening, WHO functional class, quality of life, and cardiopulmonary hemodynamic parameters. Ambrisentan appears to be safe and well tolerated, with a low incidence of acute hepatotoxicity. Ambrisentan has an improved safety profile compared with sulfonamide-class ERAs with respect to the potential for hepatic toxicity and the potential for drug-drug interactions with agents metabolized by P450 enzymes such as warfarin and sildenafil. These data support the role of ambrisentan for the treatment of PAH

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