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Pharmacological and Pharmaceutical Profile of Bosentan: A Review

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ABSTRACT

Bosentan is a dual endothelin receptor antagonist. It is used in the treatment of pulmonary artery hypertension (PAH). Endothelin receptor antagonists (ERAs) act on the endothelin pathway by blocking binding of endothelin-1 to its receptors [endothelin type-A (ET_A) and/or type-B (ET_B)] on the surface of endothelial and smooth muscle cells. Bosentan is licensed in the United States, the European Union and other countries by Actelion Pharmaceuticals for the management of PAH under the trade name Tracleer. Bosentan, is a non-peptide and orally active. Bosentan is highly protein-bound, with approximately 98% bound to albumin. This paper reviews the pharmacological and pharmaceutical properties of Bosentan. Bosentan could be an attractive target for the generic industries.

Keyword: Bosentan, Pulmonary arterial hypertension, Endothelin receptor antagonist.

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INTRODUCTION

Pulmonary hypertension is a rare disorder involving an increase of pressure in the pulmonary arteries that can be caused by a variety of factors, one of which is a chronic thrombosis in the pulmonary arteries[1]. Bosentan is a non peptide, orally active, dual endothelin receptor antagonist, is the first endothelin receptor antagonists (ERA) to be used successfully in the treatment of pulmonary artery hypertension (PAH) [2]. Endothelin receptor antagonism has emerged as an important therapeutic approach in pulmonary arterial hypertension (PAH). Bosentan is safe and improves exercise capacity over the short term in patients with Eisenmenger's physiology[3,4].

Bosentan was approved by the US Food and Drug Administration to treat pulmonary hypertension; it has been reported to improve the function of the right ventricle as well as exercise tolerance of patients. Bosentan is an endothelin-receptor antagonist that reportedly induces both cytochrome P450 (CYP) 3A4 and CYP2C9 enzymes, which are also involved in warfarin metabolism[5,6]. Bosentan, a non-selective, oral ET-1 receptor antagonist, decreases pulmonary arterial pressure and vascular resistance and improves exercise capacity or quality of life in patients with symptomatic pulmonary arterial hypertension[7]. Bosentan improves ET-1 induced imbalance of oxidative stress and nitric oxide (NO) bioavailability leading to inflammation in pulmonary arteries, which leads to the decrease in pulmonary vascular resistance and amelioration of pulmonary arterial re-modelling; however, it is unclear whether bosentan improves Systemic sclerosis (SSc)-related peripheral circulation insufficiency[8-10]. Bosentan also delayed time to clinical worsening. Sitaxsentan's and ambrisentan are selective ERAs that block the ETA receptor[11].

HISTORY OF BOSENTAN

In 1994, Martine Clozel and group at Hoffman-La-Roche (Basel, Switzerland) reported the discovery of Bosentan. Bosentan is a non-peptidic ET receptor antagonist. In receptor radioligand binding assays using recombinant human receptors expressed on Chinese hamster ovary (CHO) cells, bosentan was less discriminatory between ET_A (Ki =6.5 nM) and ET_B (Ki = 343 nM) receptor subtypes, and is therefore known as a mixed ET-receptor antagonist. Bosentan also inhibited the contractile response of isolated rat aorta to ET ($_pA_2$ = 7.2) and isolated rat trachea to sarafotoxin 6C (pA_2 = 6.7), a selective ET_B- receptor agonist. Being a low-MW synthetic compound, bosentan could be administered orally. As a result, it has been tested for efficacy not only to inhibit ET-1- induced pressor responses, but also in experimental animal models of, for example, hypertension, congestive heart failure, cerebral vasospasm and renal

failure. Bosentan was ready to enter Phase II clinical trials by 1994. However, it entered Phase III clinical development only recently for hypertension and congestive heart failure[12-16].

Physicochemical Properties of Bosentan

Bosentan is 4-tert-butyl-N-[6-(2-hydroxyethoxy)-5-(2-methoxyphenoxy)-2-(pyrimidin-2-yl) pyrimidin-4-yl] benzene-1-sulfonamide (**Figure 1**) with chemical formula $C_{27}H_{29}N_5O_6S$. It's molecular weight is 551.61 g/mol. It is Pale Yellow to Off-White Solid. Melting point of Bosentan is 107-110°C. It is poorly soluble in water (1.0 mg/100 ml) and in aqueous solutions at low pH (0.1 mg/100 ml at pH 1.1 and 4.0; 0.2 mg/100 ml at pH 5.0). Solubility increases at higher pH values (43 mg/100 ml at pH 7.5). Bosentan available as tablets formulation as tracleer, Lupibose, Bosentas (125 mg, 62.5 mg)[17,18].

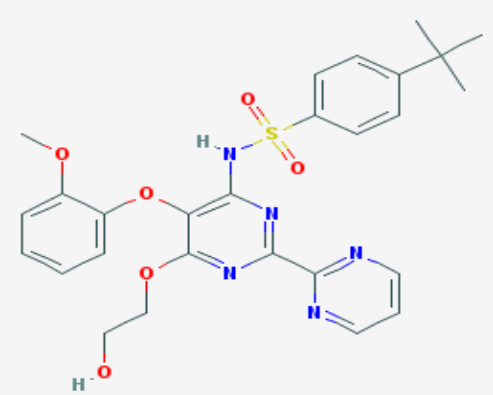

Figure 1: **Structure of Bosentan**

PHARMACOLOGICAL PROFILE:

Pharmacology

Bosentan belongs to a class of drugs known as endothelin receptor antagonists (ERAs). Patients with PAH have elevated levels of endothelin, a potent blood vessel constrictor, in their plasma and lung tissue. Bosentan blocks the binding of endothelin to its receptors, thereby negating endothelin's deleterious effects[19, 20]. Bosentan is an inducer of the CYP2C9 and CYP3A4 enzymes which may explain the increased clearance and reduced plasma levels of bosentan seen at steady-state. This induction affects the plasma levels of other compounds metabolized by these enzymes: ciclosporin, glibenclamide, simvastatin and warfarin. Specifically, simvastatin levels may be reduced by 50%; warfarin concentrations are reduced but no relevant changes in INR have been experienced. Glibenclamide and bosentan concentrations are both reduced when co-administered, and here is also an increased risk of transaminase elevation. Concomitant ciclosporin use results in a reduced ciclosporin concentration and a tripled bosentan steady-state concentration via CYP3A4. The use of ciclosporin and glibenclamide with bosentan is

contraindicated. Inhibitors of CYP2C9 (fluconazole, amiodarone) and CYP3A4 (ketoconazole, itraconazole) can be expected to increase bosentan concentration. Another important interaction occurs with oral contraceptive agents: concomitant bosentan reduced norethisterone and ethinyl estradiol levels in a pharmacokinetic study and therefore hormonal contraception cannot be relied on[21, 22].

Mechanism of Action

Endothelin-1 (ET-1) is a neuro hormone, the effects of which are mediated by binding to ET_A and ET_B receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease. Bosentan is a specific and competitive antagonist at endothelin receptor types ET_A and ET_B. Bosentan has a slightly higher affinity for ET_A receptors than for ET_B receptors[23].

PHARMACEUTICAL PROFILE

Pharmacokinetics

ERAs are orally administered direct inhibitors of ET-1 receptors. Bosentan acts non-selectively on both the ET_A and ET_B receptors (ET_A: ET_B 20:1), whereas both sitaxsentan (ET_A: ET_B 6500:1) and ambrisentan (ET_A: ET_B 260:1) are significantly more selective for the ET_A receptor. Bosentan's pharmacokinetics is dose-proportional up to 600 mg (single dose) and 500 mg (multiple doses) daily. It is dosed 62.5 mg twice a day the first 4 weeks and 125 mg twice a day thereafter. No dose adjustment is required in adults based on sex, age, bodyweight or mild hepatic impairment[24,25]. Bosentan's bioavailability is about 50%, and is similar for either a single 125 mg tablet or two 62.5 mg tablets. Concomitant intake of food does not have a significant impact on absorption.

Absorption

Bosentan's bioavailability is thought to be 50% and is similar for 125 mg tablet or with two 62.5 mg tablet. Ambrisentan is rapidly absorbed after oral administration but the bioavailability is unknown. Food has no effect on the bioavailability of ambrisentan or bosentan. Sitaxsentan's oral bioavailability is greater than 90%[26,27].

Distribution, Metabolism

Bosentan is highly protein-bound, with approximately 98% bound to albumin. It is metabolized by the hepatic cytochrome P450 (CYP) enzymes CYP3A4 and CYP2C9.18 Three metabolites are formed, one of which, Ro 48–5033, is biologically active, and may contribute to up to 20%

of the parent compound's action. The elimination of unchanged bosentan and its metabolites is primarily through the biliary system, with less than 3% excreted renally. The half-life of bosentan is 5 to 8 hours. Due to its interaction with the Cytochrome P450 enzymes, bosentan should be avoided in patients with moderate to severe liver disease or baseline liver transaminases greater than 3 times the upper limit of normal. Bosentan is extensively metabolized by the liver[21,25].

Excretion

The elimination of bosentan is primarily through the biliary system with only 3% or less excreted through the kidneys[25].

PHARMACODYNAMICS

Endothelin (ET) is a neurohormone secreted by the endothelium. It is a very potent vasoconstrictor, as well as a stimulator of cell proliferation, fibrosis and inflammation. The two receptors ET_A and ET_B are involved in the contractile effect of ET-1 in human pulmonary arteries. Recent publications suggest a beneficial effect of ET_A blockade in cardiovascular and renal disease; whereas ET_B mediated .effects may be protective in animals.

Bosentan increases ET plasma concentrations by a factor of 2-3 fold. When bosentan is given chronically, the increase in ET levels is less marked after prolonged treatment than early on. Bosentan was tested in several animal models of chronic PAH, and was either given as a preventive treatment or as a curative treatment after the establishment of PAH. In the chronic hypoxic rat model, bosentan not only prevented the development of pulmonary hypertension but also reversed established pulmonary hypertension and vascular remodelling. Bosentan has been shown to have an effect both on pulmonary vascular remodelling and the development of right ventricular hypertrophy. Bosentan inhibits the pressor effects of ET peptides on ET_A and ET_B receptors, and decreases blood pressure and peripheral vascular resistance in various rat models of hypertension without inducing tachyphylaxis. In contrast to these pathological situations, bosentan has no significant blood pressure-lowering effect of normotensive animals, with the exception of normotensive guinea pigs. The lowering of blood pressure induced by bosentan is not associated with an increase in heart rate[25].

DOSAGE AND ADMINISTRATION [5,18,28,29]

Bosentan (Tracleer), initial dose is 62.5 mg two times in a day for 4 weeks and then increased to the maintenance dose of 125 mg two times in a day is used for the treatment of Pulmonary

arterial hypertension. The dose of bosentan in children is dependent upon age and weight of person. The adult dose and child dose are summarized (**Table 1**)

Table 1: Recommended dose regimens for bosentan in adults and children

	Starting dose (1st 4-week)	**Maintenance dose (Week 5 onward)**
Adults (> 12 Years of age)		
Body weight > 40 kg	62.5 mg twice daily	125 mg twice daily
Body weight < 40 kg	62.5 mg twice daily	62.5 mg twice daily
Children (< 12 years of age)		
Body weight < 10 kg	15.6 mg daily	15.6 mg twice daily
Body weight 10-20 kg	31.25 mg daily	31.25 mg twice daily
Body weight 20-40 kg	31.25 mg twice daily	62.5 mg twice daily
Body weight > 40 kg	62.5 mg twice daily	125 mg twice daily

Special populations

Dosage in hepatic impairment

No dose adjustment is needed in patients with mild hepatic impairment. Bosentan (Tracleer) is contraindicated in patients with moderate to severe liver dysfunction.

Dosage in renal impairment

No dose adjustment is required in patients with renal impairment. No dose adjustment is required in patients undergoing dialysis.

Dosage in elderly patients

No dose adjustment is required in patients over the age of 65 years.

Renal impairment

In patients with severe renal impairment (creatinine clearance 15–30 mL/min), plasma concentrations of bosentan decreased by approximately 10%. Plasma concentrations of bosentan metabolites increased about 2-fold in these patients as compared to subjects with normal renal function. No dose adjustment is required in patients with renal impairment. There is no specific clinical experience in patients undergoing dialysis. Based on physicochemical properties and the high degree of protein binding, bosentan is not expected to be removed from the circulation by dialysis to any significant.

ADVERSE EFFECTS[5,18]

Bosentan cause serious adverse effects which are as follows:

- **Serious birth defects**: When bosentan is used in pregnancy then cause serious birth defects.
- **Fluid retention and swelling of ankles and legs**: Bosentan (Tracleer) can cause in body to hold too much water, and may get swelling of ankles and legs.

- **Lower Sperm Count**
- **Low red blood cell levels (anaemia).**

Bosentan cause most common adverse effects which are as follows:

- Nausea
- Vomiting
- Fever
- Unusual tiredness
- Stomach area (abdominal) pain
- Yellowing of the skin or the whites of your eyes (Jaundice).

Safety and tolerability

Bosentan is very well tolerated. The most common adverse effect is hepatotoxicity which results from the inhibition of a bile acid export pump by bosentan and its metabolites[30,31].

DRUG INTERACTION

Bosentan induces members of the cytochrome P450 family. Administration of bosentan therefore leads to increased metabolism of warfarin, and cyclosporin A, and HMG CoA reductase inhibitors[32,33]. Concomitant administration of bosentan and inhibitors of CYP3A4, such as the azole fungicides, can increase the peak plasma concentration of bosentan by more than 2-fold. Lastly, use of bosentan and the oral hypoglycaemic glyburide is contraindicated due a higher incidence of hepatoxicity and reduced plasma levels of both drugs.

Two additional interactions deserve special attention in the PAH patient. First is the interaction with phosphodiesterase 5 (PDE5) inhibitors. Treatment with bosentan 62.5 mg twice daily was associated with a two-fold increase in sildenafil clearance. Increasing the dose of bosentan to 125 mg twice daily led to a further increase in sildenafil oral clearance, demonstrating that bosentan, in a dose dependant manner, decreases the plasma concentration of sildenafil by as much as 55%. Similarly, in healthy volunteers, bosentan decreased tadalafil exposure by 41.5%. In addition, sildenafil significantly increases bosentan plasma levels. The clinical implication of these pharmacologic interactions remains to be documented. Second, bosentan decreases the effectiveness of hormonal oral contraceptives. Awareness of this effect is crucial for PAH patients, in whom pregnancy can induce a life-threatening pulmonary hypertensive crisis. Women of child-bearing age who are treated with bosentan must use two methods of contraception[22,34-36].

Treatment of Pulmonary Artery Hypertension (PAH)

Bosentan monotherapy in PAH

Bosentan monotherapy is indicated for patients in WHO functional class III in these conditions. Bosentan also appears to be effective in patients in WHO functional class IV but it remains unclear if it is a preferred first line therapy compared to intravenous epoprostenol, where there appears to be more evidence for intravenous epoprostenol therapy. In patients with idiopathic or familial PAH who present in WHO class IV with evidence of right ventricular dysfunction, the authors and others recommend that intravenous epoprostenol be considered as first line therapy. In those patients who are stabilized on intravenous epoprostenol, especially at low doses, it may be possible to switch them to bosentan monotherapy although this needs to be done with a very slow reduction of epoprostenol dose and concomitant monitoring[37,38].

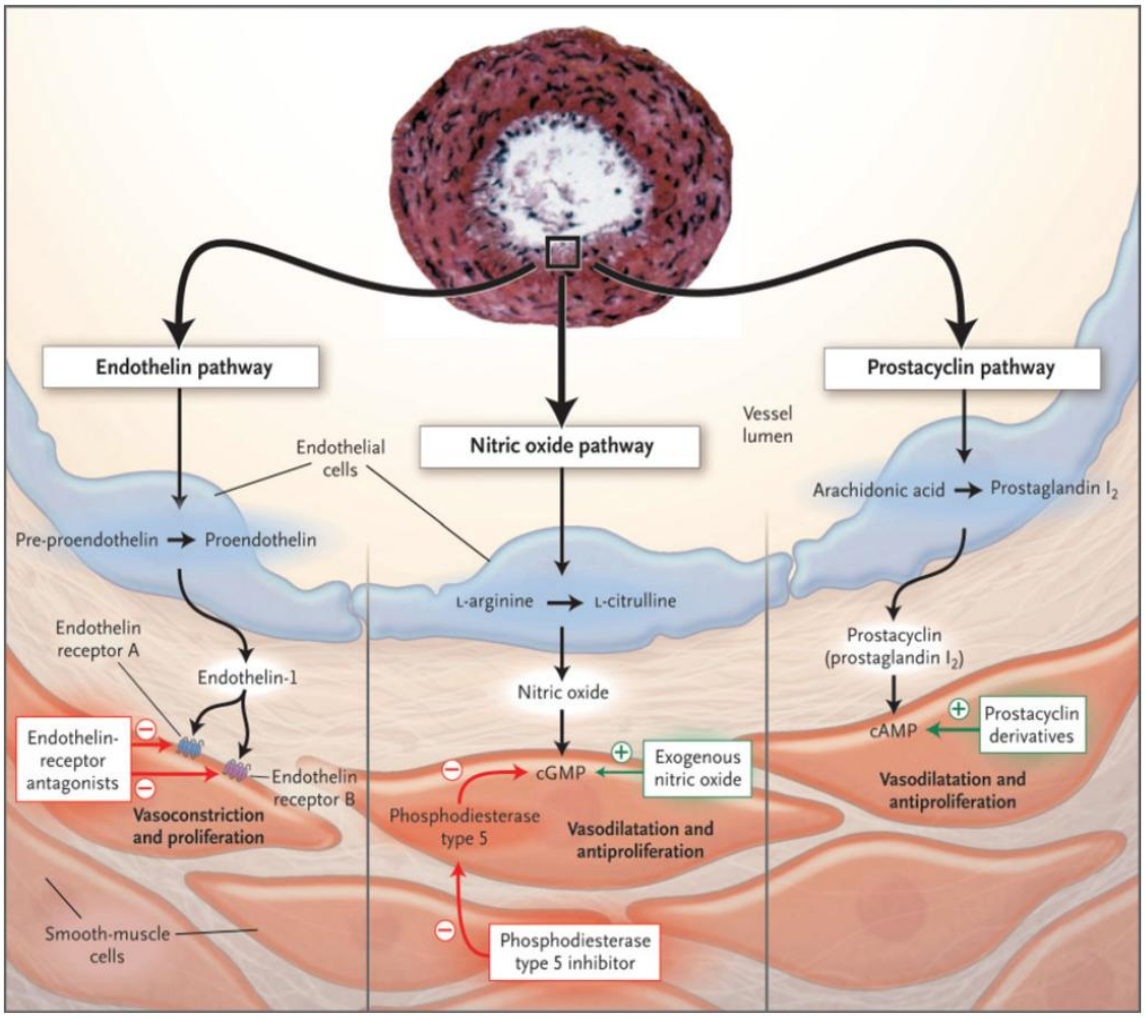

Figure 2 Postulated pathways in the pathobiology of pulmonary arterial hypertension (PAH)

Specific PAH therapies

In recent years, the development of specific PAH therapies has increased the options available to the clinician managing a patient with PAH. There are four main classes acting upon three main

intracellular pathways these currently available specific PAH therapies aim to redress the imbalance in mediators which occur as a result of endothelial cell dysfunction. This imbalance consisting of reduced production of prostacyclin and nitric oxide and upregulation of ET-1 resulting in the abnormal proliferation and contraction of pulmonary smooth muscle cells via three pathways, all of which are potential targets for therapy (**Figure 2**)[39].

Role of Bosentan in connective tissue disease associated PAH

PAH can complicate all forms of connective tissue disease. Most commonly it complicates systemic sclerosis (scleroderma) especially the limited cutaneous subtype. PAH can complicate up to 25% of patients with limited cutaneous scleroderma. PAH can also complicate SLE, mixed connective tissue disease and less commonly, rheumatoid arthritis. the results with bosentan (or any other specific PAH therapy) have not been as impressive with scleroderma associated PAH when compared to idiopathic PAH. This most probably reflects a different pathogenesis, older age of patients and that these patients tend to present later in their disease course[40].

Bosentan combination therapy in PAH

PAH patient quality of life and survival remains poor despite the tremendous medical advances with monotherapy. The desire to further improve quantity and quality of life has led to the study of combination therapy. Bosentan has been used in combination with other several classes of PAH therapies, specifically prostacyclin analogues and PDE5 inhibitors. The bosentan have resulted in significant improvements in exercise capacity, cardiopulmonary hemodynamics and survival. However, responses are variable and in many patients, disease progresses despite therapy. As a result an increasing number of patients are being considered for combination therapy. Current therapies in the treatment of PAH act on the three intracellular pathways, endothelin, nitric oxide and prostacyclin, known to be abnormal in PAH (**Figure 2**). A logical extension therefore is to use a combination of two or more therapies acting in synergy through a different pathway. The combination of bosentan and sildenafil is of particular interest because both are oral agents, which are generally well tolerated[41,42].

CONCLUSION

The dual endothelin receptor antagonist bosentan given at a dose (in adults) of 62.5 mg twice daily for four weeks followed by 125 mg twice daily is a safe and efficacious therapy in PAH. The use of bosentan as part of a comprehensive management plan has resulted in improvements in exercise capacity, functional class, quality of life and survival. Patients require regular monthly monitoring of liver function tests and clear guidelines are in place in terms of reducing

or stopping bosentan therapy depending upon the results of these liver function tests. Because of bosentan's ability to induce the cytochrome p450 family, patients must be advised to contact their treating physician before initiation of other prescription medicines including oral contraceptives and antibiotics. Bosentan has been extensively used as monotherapy in PAH especially in patients with idiopathic PAH and scleroderma associated PAH but also appears to be efficacious in other forms of pulmonary hypertension including other connective tissue disease associated PAH.. Bosentan may also have a role as part of combination therapy in patients who have responded sub optimally to monotherapy. So Bosentan could be an attractive target for the generic industries.

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