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Research Article

Bosentan, Ambrisentan, and Macitentan: Practical Therapeutics

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ABSTRACT

Endothelin receptor blockers are the mainstay of treatment for pulmonary arterial hypertension. These drugs produce pulmonary vasodilation and reduce smooth muscle proliferation by blocking endothelin receptors on pulmonary vascular smooth muscles. Bosentan is the most studied and most widely used endothelin receptor blocker. It is the only drug of this class which is approved for use in children. Nonetheless, better side effect profile and cost effectivity has prompted many to prefer ambrisentan and macitentan over bosentan. This review focuses on the practical aspects of bosentan, ambrisentan and macitentan therapeutics.

Keywords: Endothelial receptor antagonists; Pulmonary arterial hypertension; Precapillary pulmonary hypertension

INTRODUCTION

Bosentan, ambrisentan and macitentan are endothelin receptor antagonists (ERA) approved for the treatment of pulmonary arterial hypertension (PAH). Several well-conducted clinical trials and post marketing surveillance have established the safety and efficacy of these drugs both as monotherapy and part of combination therapies [1–6]. The potential use of ERA in several other disorders like cancer, fibrosis, renal disease and pain management is under investigation [7].

For the purpose of this review article, we searched Medline and Google scholar for published English literature focussing on the practical therapeutics of ERAs. We applied the search strategy using keywords "Endothelin receptor antagonists" paired with "practical usage", "pharmacokinetics', pulmonary arterial hypertension, " adverse effects", "Eisenmenger syndrome", "combination therapy", "human immunodeficiency virus (HIV)", "connective tissue disease", "left heart disease" "chronic lung disease", "porto-pulmonary hypertension" and "cost-effectiveness." The search in MEDLINE and Google scholar databases resulted in 1876 articles including clinical trials, reviews and systematic reviews. The title and abstracts of these articles were scanned. The studies related to pulmonary vasodilators other than bosentan, ambrisentan and macitentan and clinical reviews published before last 10 years were excluded. Keeping the practical aspects in focus, 46 articles were chosen for the review.

MECHANISM OF ACTION AND RELEVANT PHARMACOKINETICS

Endothelin pathway plays a major role in the pathophysiology of pulmonary hypertension. Endothelin-1 is a vasoactive peptide produced by pulmonary vascular endothelium and has an important role in the pathogenesis of PAH. It acts on Endothelin A (ETA) and Endothelin B (ETB) receptors located on the pulmonary smooth muscle vasculature and mediate vasoconstriction and smooth muscle proliferation (Figure 1). The ETB receptors present on the pulmonary vascular endothelium mediate vasodilatation (7). Bosentan and macitentan are non-selective ETA and ETB blockers, while ambrisentan is a selective ETA receptor blocker. In effect, ERAs cause vasodilation and reduce proliferation of the pulmonary vessels [8].

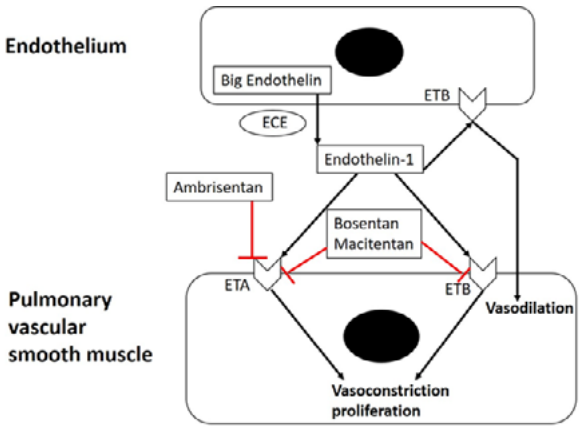

Figure 1: Mechanism of action of bosentan, ambrisentan and macitentan ECE endothelin converting enzyme, ETA endothelin a receptor, ETB endothelin B receptor.

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Ambrisentan and macitentan have higher bioavailability and longer half-life when compared to bosentan (Table 1). Bosentan has shorter half-life requiring twice a day dosing compared to ambrisentan and macitentan which are given once daily. The cytochrome P450 system of enzymes plays a role in the metabolism of these drugs, making these agents prone to drug interactions. Bile salt transport proteins are involved in the elimination of bosentan and are responsible for increased hepatoxicity of bosentan amongst the group [9].

Table 1: Pharmacokinetics of bosentan, ambrisentan and macitentan, CYP cytochrome P450; OATP organic anion transport protein; Tmax time to reach peak plasma concentration; T ½ half-life; UGT uridine 5'5' diphosphate glucuronosyl transferase.

Parameter	Bosentan [9]	Ambrisentan [9]	Macitentan [10]
Route of administration	Oral	Oral	Oral
Bioavailability (%)	50%	80%	74%
Tmax (hours)	3	2	8
T½ (hours)	5	15	16
Protein binding (%)	98	99	>99
Elimination pathway	Hepatic, biotransformation	Hepatic, biotransformation	Renal, biotransformation
Enzymes involves in metabolism	CYP3A4 and CYP2C9, OATP	CYP3A4, CYP2C19, UGT	CYP3A4

INITIATION OF THERAPY

Indication

ERAs are indicated in pre-capillary and combined pre and post-capillary hypertension. Robust evidence exists regarding the use of these drugs in WHO group 1 pulmonary arterial hypertension (PAH) including idiopathic PAH (IPAH), hereditary PAH (HPAH) and PAH associated with connective tissue disorder, HIV and congenital heart disease [1-4,10]. Increasing amount of evidence demonstrates their usefulness in other WHO groups of PAH also (Table 2). ERAs are not effective in isolated post capillary hypertension and may even be harmful [11,12].

Table 2: Role of ERAs in specific pulmonary hypertension subsets

PAH group	Role of ERA	Available evidence
Connective tissue disease (CTD)	Same as in IPAH	RCTs including CTD patients showed improvement in 6MWD and haemodynamics when compared to placebo but lesser than PDE5i and prostanoids and less effective than in IPAH patients [13,14].
Portal Hypertension	Bosentan harmful, ambrisentan and macitentan can be used in moderate liver disease	PORTICO trial (macitentan) and an open label RCT in (ambrisentan) showed efficacy and safety in PoPH with moderate hepatic dysfunction [15,16].
HIV	Same as IPAH with drug interactions taken into account	Open label prospective and retrospective studies of bosentan, sporadic patients in ARIES and SERAPHIN trials showed clinical and hemodynamic benefit [17].
Pulmonary veno-occlusive disease	Cautious use; can lead to drug induced pulmonary oedema	Case reports [18]
Left heart disease	Insufficient evidence for use	ENABLE- 1,2 (bosentan) and MELODY (macitentan) trials showed worsening heart failure [12].
Lung disease (COPD, IPF, ILD)	May be used in severe PAH and predominantly hemodynamic phenotype	Insufficient evidence; several trials of bosentan, ambrisentan and MUSIC (macitentan) trial showed no benefit. Ambrisentan (ARTEMIS IPF) lead to disease progression in IPF [19,20].
CTEPH	Can be used in inoperable cases; riociguat preferred	BENEFiT (bosentan) trial, AMBER (ambrisentan) and MERIT-1 (macitentan) trials showed reduction in PVR [21,22].

Note:COPD chronic obstructive pulmonary disease; CTEPH chronic thromboembolic pulmonary hypertension; HIV human immunodeficiency virus; ILD interstitial lung disease; IPAH idiopathic pulmonary arterial hypertension; IPF idiopathic pulmonary fibrosis; PDE5i phosphodiesterase inhibitors; PoPH pulmonary hypertension associated with portal hypertension; RCT randomised controlled trial.

PAH specific drug therapy is recommended from WHO functional class II onwards, either as monotherapy or in combination. ERAs are initiated when pulmonary vasculature is non-reactive on acute vasoreactivity testing in WHO groups 1 of PAH. In other groups, the vasoreactivity testing results may be unreliable and hence is not recommended. In WHO group 3 of pulmonary hypertension (associated with chronic lung disease), ERA are indicated in patients with PH disproportionate to hypoxia lung function. Hence, a right heart catheterisation study is recommended to confirm the diagnosis and establish severity [13].

Non-Ph use of era

Preclinical studies have demonstrated promising antiproliferative effect of ERA in various types of cancer, however clinical trials have not replicated the beneficial results so far. A few animal studies and small clinical trials have shown reduction of proteinuria and cardiovascular risk in patients with chronic kidney disease and diabetic nephropathy by ERA. However, larger studies are required to recommend their use in clinical practice. Bosentan is also proven to be useful in reducing digital ulcers in patients with systemic sclerosis [7].

Choice of drug

Ambrisentan being selective ETA receptor blocker has the advantage of preserving the vasodilatory properties of ETB receptors on endothelial cells when compared to non-selective bosentan and macitentan [9]. Increased tissue penetration and slow dissociation of macitentan has been cited as the reason for better efficacy compared to bosentan [1,8]. Moreover, higher incidence of adverse events of bosentan makes it lesser preferable amongst the group.

A network metanalysis, comparing the efficacy and safety of bosentan, ambrisentan and macitentan with each other, showed that bosentan was most efficacious in terms of highest mean change in 6-minute walk distance (6MWD) (mean 52.67 m) and lowest odds ratio (OR) for clinical worsening (mean OR 0.35) with ambrisentan being the close second (6MWD change mean 42.31 m, clinical worsening mean OR 0.30) when compared to placebo [14,15]. But ambrisentan was found to be better in terms of safety profile. Therefore in combined analysis of efficacy and adverse effects profile, ambrisentan was concluded to be the drug of choice. Macitentan being a relatively newer molecule, has been tested only in few trials. The efficacy of macitentan is evident by SERAPHIN trial, which showed reduction in long-term morbidity and mortality and risk of hospitalization related to pulmonary hypertension and improvement in heath related quality of life [1]. Hence, macitentan can be considered as an efficacious alternative. With several ongoing trials, the evidence for macitentan is expected to grow in future [16].

COMBINATION THERAPY OR MONOTHERAPY

Bosentan, ambrisentan and macitentan have been used in various combinations with other PAH specific drug therapies like phosphodiesterase 5 inhibitors (PDE5i) and prostanoid group of drugs. They can be combined upfront (at initiation of therapy) or sequentially. The European Society of Cardiology (ESC) recommends monotherapy for low risk patients (WHO functional class I, II) and combination therapy for intermediate and high-risk categories (WHO functional class III, IV) [17]. These categories have been defined based on signs and symptoms of right heart failure, functional class, 6MWD, echocardiography and hemodynamic assessment. The AMBITION trial demonstrated the advantage of upfront combination of ambrisentan and tadalafil over either drug as monotherapy [18]. Based on these results, 2019 American chest physician guidelines recommend initiating combination therapy in WHO functional class II and III; and in class IV if the patient is intolerant or unwilling to use intravenous epoprostenol. Ongoing OPTIMA trial evaluating an initial combination therapy with macitentan and tadalafil has also shown promising preliminary results [19,20]. Evidence for initial combination therapy of ERA with prostanoid group is not very strong so as to be recommended as first line therapy [21,22]. Sequential or add-on therapy has been tried in various combinations of different groups and has shown beneficial results [23,24]. The GRIPHON trial demonstrated 34% risk reduction of disease progression and hospitalization by sequential addition of Selexipag, an oral prostacyclin receptor agonist to endothelin receptor antagonist therapy and is a recommended combination [25,26,27]. Drug therapy can be escalated to dual and triple drug combination for goal directed treatment based on various treatment targets monitored routinely [24].

Role in Eisenmenger Syndrome (Es) and other groups of pulmonary hypertension

Bosentan is shown to be effective in Eisenmenger syndrome (ES) [28]. A retrospective cohort study of ambrisentan in 38 patients with ES demonstrated improvement in 6MWD and no serious adverse effects were observed [29]. No trial has evaluated the role of ambrisentan in ES so far. MAESTRO trial evaluated macitentan in ES and failed to show it's efficacy [30]. The possible reasons of lack of effect of macitentan in this trial are marked improvement of primary outcome (6MWD) in placebo arm and improper technique of 6MWD in the smaller centres involved in the trial [30].

DOSAGE AND TITRATION

Initiation of therapy

The adverse effects like headache, muscle pain and dizziness are common at the time of initiation especially when started at high doses and combined with other vasodilator drugs like phosphodiesterase [2]. Staggered initiation is practiced in several PAH centres in which the second drug is initiated after two to four weeks. Staggered initiation allows the patient to adapt to the vasodilator effect of one drug and improves tolerability [31] (Table 3).

Table 3: Recommended doses for adult and paediatric population

Drug	Adult dose [23]	Paediatric dose
Bosentan	125 mg twice daily	Initial dose: 0.3–1 mg/kg per dose twice daily
		<10 kg- 2 mg/kg per dose twice daily
		10–20 kg- 2 mg/kg per dose twice daily
		20–40 kg- 62.5 mg per dose twice daily
		> 40 kg -125 mg per dose twice daily [32]
Ambrisentan*	5 or 10 mg once daily	<20 kg -2.5 mg to 5 mg once daily
		20-40 kg- 5 mg once daily
		>40 kg -5 mg to 10 mg once daily [33]
Macitentan	10 mg once daily	No published data

TITRATION

A gradual up-titration also enhances the tolerability of therapy. In BREATHE-5 trial of bosentan in patients with Eisenmenger syndrome, patients were initiated at a lower dose of 62.5 mg twice daily and increased four weeks later to 125 mg twice daily [11]. In AMBITION trial, both tadalafil and ambrisentan were started at half the recommended doses and at four weeks tadalafil was doubled to maximum dose and was increased to full dose at eight weeks [32,33].

ADVERSE EFFECTS

A meta-analysis of nearly 5000 patients compared the safely profile of bosentan, ambrisentan and macitentan. Hepatoxicity, peripheral oedema and anaemia were the major adverse effects reported for all the three drugs [34]. Bosentan was reported to have the highest hepatoxicity amongst the group (12.3% versus 2.47 %; p <0.0001) when compared to placebo. Hepatotoxicity is caused by inhibition of bile salt protein involved in the metabolism of bosentan. Both ambrisentan and macitentan did not show significant hepatoxicity compared to placebo. Hence, Food and Drug Administration (FDA) removed the requirement of monthly liver function test (LFT) for ambrisentan in 2011 which led to significantly reduced testing for liver function and expenditure [35]. However, a post marketing surveillance data in 718 patients on macitentan showed 3.9% rate of ≥ 1 hepatic events [5]. Ambrisentan (20.8% vs 10.3%; p=0.0002) and bosentan (10.3% versus 7.1%; p=0.02) conferred increased risk of peripheral oedema whereas macitentan (9.98% versus 3.7%; p=0.0004) and bosentan (4.72% versus 2.01%; p=0.002) increased the risk of anaemia compared to placebo [34]. Increased vasopressin levels and sodium retention at renal tubules caused by ERAs is the likely mechanism of peripheral oedema as well as dilutional anaemia [1,34].

The minor adverse effects often cause significant discomfort and lead to discontinuation of drugs (Table 4) [1,2,11,29]. Combination therapy can further increase the rate of adverse effects as demonstrated by the AMBITION trial. The rate of peripheral edema, anaemia, nasal congestion, dizziness and headache was higher with the combination of ambrisentan and tadalafil compared to monotherapy with any of the two drugs however the rate of discontinuation remained the same in combination therapy and monotherapy in the trial [2].

Table 4. Adverse effects of Endothelin receptor antagonists

Major adverse effects	Minor adverse effects*
Transaminase elevation	Headache, dizziness, syncope
Anaemia	Upper and lower respiratory tract infections, nasopharyngitis, sinusitis
Peripheral oedema	Diarrhoea, nausea, vomiting, dyspepsia
	Cough, flushing, dyspnoea, palpitation
	Muscle pain, arthralgia, back pain, non-cardiac chest pain, fatigue

Note:*In decreasing order of requency in randomised trials

Management of adverse effects

Headache and muscle pain can be managed with temporary dose reduction and if PDE5i are co-administered, PDE5i dose should be reduced. These adverse effects usually subside after one week [31]. Drug induced peripheral oedema does not warrant any specific measure once worsening congestive heart failure is ruled out; occasionally leading to discontinuation of therapy. Drug induced anaemia, seen more commonly with macitentan, usually occurs in the initial phase of therapy and is aggravated in pre-existing anaemia. The intervention arm of MAESTRO trial with macitentan showed a mean reduction of 1.04±1.37 g%, and about one-third of patients had ≥ 2 g% fall in haemoglobin. In SERAPHIN trial, 4.3% patients had fall in haemoglobin <8 g/dL [1,28]. Monitoring of haemoglobin is recommended monthly, as haemoglobin stabilises by first four weeks of therapy [1,30]. If asymptomatic elevation of transaminases develops, transient discontinuation is warranted if two serial values of transaminases are ≥ 3 times the upper limit of normal (ULN). Hepatic encephalopathy, bilirubin elevation ≥ 2 times ULN and transaminases ≥ 8 times ULN warrant permanent discontinuation [35,36].

DRUG INTERACTIONS AND COMORBIDITIES

Drugs that induce or inhibit CYP3A4 enzyme can potentially interact with bosentan, ambrisentan and macitentan but ambrisentan is least affected as it is predominantly metabolised by UGT enzyme (Table 5) [9]. Macitentan has been reported to have fewer interactions but requires further evaluation [5]. Drug interactions are particularly important when using ERAs in patients with HIV, connective tissues disorders, other vasodilators like nitrates used in coronary artery

disease [31].

Table 5: Clinical significance of reported drug interactions of bosentan, ambrisentan and macitentan

Drug of interaction Bosentan	Clinical significance [5,9,24]
Sildenafil	No dose adjustment required
Cyclosporine	Contraindicated; severe hepatoxicity
Glibenclamide	Contraindicated; severe hepatoxicity, impaired sugar control
Amiodarone	Contraindicated; severe hepatoxicity
Warfarin	Intensified monitoring required
Hormonal contraceptives	Alternative method of contraception required
HMG CoA reductase inhibitors	Cholesterol level monitoring, drug level reduced
Rifampin, phenytoin	No dose adjustment required; reduce Bosentan level
Fluconazole, Ketoconazole	Contraindicated; severe hepatoxicity
Erythromycin	No dose adjustment required for short course
Ritonavir, saquinavir, lopinavir	Dose adjustment required, increase bosentan level
Ambrisentan	
Cyclosporine, ketoconazole	Caution recommended; potential hepatoxicity
Macitentan	
Ketoconazole, rifampin	Should be avoided

Monitoring therapy

The goals of monitoring include timely detection of adverse events, harmful drug interactions and effectiveness of therapy (Table 6). Monitoring can be done from physician's office, telephonically by healthcare worker or home monitoring in combination for optimal patient management [37].

Table 6: Parameters for monitoring drug therapy and their frequency

Parameter	Frequency
Clinical assessment, weight	Should be avoided
gain	Baseline,1 month, then 3-6 monthly, 3 months after change in therapy, whenever clinical worsening [24]
CBC, creatinine, LFT	Same as above; monthly LFT for children on bosentan [32]
Other tests for PAH*	Same as above; for early goal directed additional therapy
PT/INR	Strict monitoring in view of interaction with warfarin
Home monitoring -weight	Daily; to report if > 2 kg at a time [31]

Note:CBC complete blood counts; INR international normalised ratio; LFT liver function test; PAH pulmonary arterial hypertension; PT prothrombin time *Includes signs of right heart failure, syncope, functional class, 6MWD, cardiopulmonary exercise testing, imaging, hemodynamic assessment

CONTRAINDICATIONS

Ambrisentan, bosentan and macitentan are category X drugs as per FDA in pregnancy and lactation. Pregnancy must be ruled out in women of child bearing age before initiation of therapy [36]. Bosentan should not be administered to patients with moderate or severe hepatic dysfunction [9]. A few studies of ambrisentan and macitentan reported no hepatoxicity in patients with Child Pugh class A and B [15,16]. These drugs should be avoided in severe hepatic dysfunction. Bosentan can be given safely in renal impairment. Ambrisentan and macitentan can be administered up to creatinine clearance of 20 mL/min but data is limited in severe renal impairment and hence should be avoided [9,36]. These drugs are not recommended in isolated post capillary hypertension.

COST EFFECTIVENESS AND OTHER PRACTICAL ASPECTS

In a systematic review of cost effectiveness, ambrisentan and sildenafil were shown to be more cost effective than bosentan [38]. Once a day therapy in ambrisentan and macitentan may improve compliance. However, the individual costs vary widely in different countries.

The cost of therapy of ERAs is higher than the PDE5i (Table 7). However, there is insufficient data to prove the efficacy and safety of ERAs over PDE5i or vice versa [39,40]. Therefore, if monotherapy is initiated, for WHO FC I and II, PDE5i may be considered as an alternative based on tolerability.

Bosentan, ambrisentan and macitentan are available as film coated and enteric coated formulations. The availability of dispersible formulation of 32 mg may be limited in the developing countries. Hence, the available preparations have to be dissolved in water before administration to children. The enteric coated tablets should not be broken. No interaction with food has been reported.

Transition from Bosentan to Ambrisentan/Macitentan

Switch from bosentan to ambrisentan or macitentan was demonstrated to be safe and effective in 87.5 % patients in SCOBA-PH trial (ambrisentan) and few observational studies of macitentan with a few showing improvements in functional class and PH after switch [5,41,42]. Lack of improvement with bosentan, once daily dosing, cost effectiveness and improved safety profile are the reasons to change to ambrisentan or macitentan. Tapering or overlap is not required and abrupt switch is tolerated [43-46].

THERAPY IN CHILDREN

Several open label randomised trials have evaluated bosentan in children age <12 years (Table 8). FDA and European Medicines Agency (EMA) have approved bosentan for PAH in children older than 1 year of age at the daily dose of 4 mg/kg [32]. Monthly LFT is

recommended in children although post marketing surveillance data shows lower incidence of hepatitis and anaemia in children (<12 years) compared to adults (2.7% vs 7.8%) [6,32] There is insufficient evidence for ambrisentan and macitentan in this population.

DISCUSSION

Increased receptor affinity and increased lipophilicity was obtained by replacing the sulfonamide moiety present in bosentan with a sulfamide moiety. Macitentan has a compact conformation facilitating deep penetration into the receptor and allowing precise occupation of a hydrophobic pocket in the ETA receptor. ET1 acts as a tissular (paracrine or autocrine) factor, therefore an ERA that can easily penetrate tissue is more potent to increase ET receptor blockade. Optimization of the ability to target the tissue has been achieved by optimization of physiochemical properties of the molecule.

CONCLUSION

Bosentan, ambrisentan and macitentan have been proven to be safe and effective drugs in the armamentarium for PAH. Ambrisentan and macitentan are preferable over bosentan in view of their safety profile, efficacy, better compliance and cost effectiveness. Bosentan is the only drug in the group proven to be useful for Eisenmenger syndrome and children in randomised trials until results of several ongoing trials of other drugs are available. Combination therapy with ERAs is the recommended regimen for PAH.

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REFERENES

1. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med. 2013;369(9):809–818.
2. Rubin LJ, Badesch DB, Barst RJ, Galiè N, Black CM, Keogh A, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346(12):896–903.
3. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, et al. Ambrisentan for the treatment of pulmonary arterial hypertension. Circulation. 2008;117(23):3010–3019.
4. Galiè N, Beghetti M, Gatzoulis MA, Granton J, Berger RMF, Lauer A, et al. Bosentan therapy in patients with Eisenmenger syndrome: A multicentre, double blind, randomized, placebo controlled study. Circulation. 2006;114(1):48–54.
5. Galiè N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med. 2015;373(9):834–844.
6. Wong AK, Channick RN. Safety and tolerability of macitentan in the management of pulmonary arterial hypertension: An update. Drug Healthc Patient Saf. 2019;11:71–85.
7. Beghetti M, Hoeper MM, Kiely DG, Carlsen J, Schwierin B, Segal ES, et al. Safety experience with bosentan in 146 children 2-11 years old with pulmonary arterial hypertension: Results from the European Postmarketing Surveillance program. Pediatr Res. 2008;64(2):200–204.
8. Enevoldsen FC, Sahana J, Wehland M, Grimm D, Infanger M, Krüger M. Endothelin receptor antagonists: Status quo and future perspectives for targeted therapy. J Clin Med. 2020;9(3) 824.
9. Correale M, Ferraretti A, Monaco I, Grazioli D, Di Biase M, Brunetti ND. Endothelin receptor antagonists in the management of pulmonary arterial hypertension: Where do we stand? Vasc Health Risk Manag. 2018;14:253–264.
10. Venitz J, Zack J, Gillies H, Allard M, Regnault J, Dufton C. Clinical pharmacokinetics and drug interactions of endothelin receptor antagonists in pulmonary arterial hypertension. J Clin Pharmacol. 2012;52(12):1784–1805.
11. Bedan M, Grimm D, Wehland M, Simonsen U, Infanger M, Krüger M. A focus on macitentan in the treatment of pulmonary arterial hypertension. Basic Clin Pharmacol Toxicol. 2018;123(2):103–113.
12. Barnett CF, De MT. Pulmonary hypertension associated with left sided heart disease. Heart Fail Clin. 2012;8(3):447–459.
13. Condliffe R, Howard LS. Connective tissue disease associated pulmonary arterial hypertension. F1000Prime Rep. 2015;7:06
14. Kuwana M, Watanabe H, Matsuoka N, Sugiyama N. Pulmonary arterial hypertension associated with connective tissue disease: Meta-analysis of clinical trials. BMJ Open. 2013;3(8): e003113.
15. Preston IR, Burger CD, Bartolome S, Safdar Z, Krowka M, Sood N, et al. Ambrisentan in porto pulmonary hypertension: A multicentre, open-label trial. J Heart Lung Transpl. 2020;39(5):464–472.
16. Krowka MJ. Treatment of porto-pulmonary hypertension with macitentan in patients with cirrhosis. Gastroenterol Hepatol (N Y). 2019;15(2):108–110.
17. Chinello P, Petrosillo N. Pharmacological treatment of HIV-associated pulmonary hypertension. Expert Rev Clin Pharmacol. 2016;9(5):715–725.
18. Montani D, Lau EM, Dorfmüller P, Girerd B, Jaïs X, Savale L, et al. Pulmonary veno-occlusive disease. Eur Respir J. 2016;47(5):1518–1534.
19. Raghu G, Million Rousseau R, Morganti A, Perchenet L, Behr J. MUSIC Study Group. Macitentan for the treatment of idiopathic pulmonary fibrosis: The randomised controlled

MUSIC trial. Eur Respir J. 2013;42(6):1622–1632.

20. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53(1):1801914

21. Ghofrani HA, Simonneau G, D'Armini AM, Fedullo P, Howard LS, Jaïs X, et al. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): Results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. Lancet Respir Med. 2017;5(10):785–794.

22. Hoeper MM. Pharmacological therapy for patients with chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2015;24(136):272–282.

23. Klinger JR, Elliott CG, Levine DJ, Bossone E, Duvall L, Fagan K, et al. Therapy for pulmonary arterial hypertension in adults: Update of the CHEST Guideline and Expert Panel Report. Chest. 2019;155(3):565–586.

24. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015;46(4):903–975.

25. Duo Ji MM, Long ZW. Comparative efficacy and acceptability of endothelin receptor antagonists for pulmonary arterial hypertension: A network meta-analysis. Int J Cardiol. 2017;234:90–98.

26. Sitbon O, Canuet M, Picard F, Gregoire P, Bergot E, Cottin V, et al. Initial treatment combination with macitentan and tadalafil in patients with pulmonary arterial hypertension: Results from the OPTIMA study. Chest. 2019;156(4): A870– A871.

27. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med. 2015;373(26):2522–2533.

28. Li Q, Kuang HY, Wu YH, Lu TW, Yi QJ. What is the position of pulmonary arterial hypertension specific drug therapy in patients with Eisenmenger syndrome: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(20): e15632.

29. Zuckerman WA, Leaderer D, Rowan CA, Mituniewicz JD, Rosenzweig EB. Ambrisentan for pulmonary arterial hypertension due to congenital heart disease. Am J of Cardiol. 2011;107(9):1381–1385.

30. Gatzoulis MA, Landzberg M, Beghetti M, Berger RM, Efficace M, Gesang S, et al. Evaluation of macitentan in patients with Eisenmenger syndrome. Circulation. 2019;139(1):51–63.

31. Burks M, Stickel S, Galiè N. Pulmonary arterial hypertension: Combination therapy in practice. Am J Cardiovasc Drugs. 2018;18(4):249–257.

32. Hansmann G, Apitz C. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network endorsed by ISHLT and DGPK. Heart. 2016;102: ii67-ii85.

33. Takatsuki S, Rosenzweig EB, Zuckerman W, Brady D, Calderbank M, Ivy DD. Clinical safety, pharmacokinetics, and efficacy of ambrisentan therapy in children with pulmonary arterial hypertension. Pediatr Pulmonol. 2013;48(1):27–34.

34. Wei A, Gu Z, Li J, Liu X, Wu X, Han Y, et al. Clinical adverse effects of endothelin receptor antagonists: Insights from the meta-analysis of 4894 patients from 24 randomized double blind placebo controlled clinical trials. J Am Heart Assoc. 2016;5 (11): e003896.

35. Durst LA, Carlsen J, Kuchinski M, Harner L, Neves D, Harris SJ, et al. Impact of the removal of the monthly liver function test requirement for ambrisentan. Am Health Drug Benefits. 2012;5(2):94–101.

36. Drugs@FDA: FDA-Approved Drugs U.S. Food and Drug Administration (FDA).

37. Dawson A, Reddecliffe S, Coghlan C, Schreiber BE, Coghlan JG. Safety and feasibility audit of a home based drug transitioning approach for patients with pulmonary arterial hypertension: An observational study. Eur J Cardiovasc Nurs. 2018;17(7):612–8.

38. You R, Qian X, Tang W, Xie T, Zeng F, Chen J, et al. Cost effectiveness of bosentan for pulmonary arterial hypertension: A systematic review. Can Respir J. 2018 Nov 18;2018: 1015239.

39. Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. Cochrane Database Syst Rev. 2019 Jan 31;1:CD012621.

40. Pharmacoeconomic Review Report: Selexipag (Uptravi) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Sep. APPENDIX 1, Cost Comparison.

41. Search Drug Information, Interactions, Images, Dosage & Side Effects | CIMS India

42. Bourge RC, Pamboukian SV, Tallaj JA, Smallfield MC, Acharya D, Iturrizaga JC, et al. The safely change from bosentan to ambrisentan in pulmonary hypertension (SCOBA-PH) study. In: B64 Management of Pulmonary Hypertension [Internet]. American Thoracic Society; 2013: A3299–A3299.

43. Barst RJ, Ivy D, Dingemanse J, Widlitz A, Schmitt K, Doran A, et al. Pharmacokinetics, safety, and efficacy of bosentan in paediatric patients with pulmonary arterial hypertension. Clin Pharmacol Ther. 2003 Apr;73(4):372–382.

44. Beghetti M, Haworth SG, Bonnet D, Barst RJ, Acar P, Fraisse A, et al. Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: The FUTURE-1 study. Br J Clin Pharmacol. 2009;68(6):948–955.

45. Berger RMF, Haworth SG, Bonnet D, Dulac Y, Fraisse A, Galiè N, et al. FUTURE-2: Results from an open-label, long-term safety and tolerability extension study using the paediatric formulation of bosentan in pulmonary arterial hypertension. Int J Cardiol. 2016 ;202: 52–58.

46. Berger RMF, Gehin M, Beghetti M, Ivy D, Kusic-Pajic A, Cornelisse P, et al. A bosentan pharmacokinetic study to investigate dosing regimens in paediatric patients with pulmonary arterial hypertension: FUTURE-3. Br J Clin Pharmacol. 2017;83(8):1734–1744.