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A Review on Drug of Pediatric Pulmonary Arterial Hypertension (PAH), their Chemistry and Pharmaceutical Dosage Forms

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ABSTRACT

Hypertension, specifically pulmonary hypertension, is a syndromethat can affect pediatric patients as well as adults. Pulmonary arterial hypertension (PAH) in pediatric patients, while rare, can be a lifethreateningcondition. There is no cure for PAH, only treatment options forchildren that are largely based on the results of adult studies. These therapies, however, can improve quality of life and survival. Treatment can be challenging because of the less approved medications and tolerable dosage forms for pediatric patients. Pediatric pulmonary arterial hypertension (PAH) shares common features of adult disease, but is associated with several additional disorders and challenges that require unique approaches. Current classes of medications primarily used to treat pediatric hypertension include phosphodiesterase inhibitors, endothelin receptor antagonists, and prostacyclins. Additional agents that may be utilized in selected pediatric patients include calcium channel blockers, anticoagulants, and inhalednitric oxide. Updates are provided on issues related to utility of the previous classification system to reflect pediatric-specific aetiologies and approaches to medical and interventional management of PAH. Also updates are provided about currently available drug substance and their details, pharmaceutical dosage forms and their details along with the mechanism of action, pharmacokinetics of the drug. These emerging data are improving the identification of appropriate targets for goal-oriented therapy inchildren. Such data will likely improve future advanced pharmaceutical dosage development and product design to enhance outcomes in pediatric PAH.

Keywords: Pulmonary arterial hypertension, pediatric hypertension, PAH

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INTRODUCTION

Pulmonary arterial hypertension is a rare blood vessel disorder of the lung in which the pressure in the pulmonary artery (the blood vessel that leads from the heart to the lungs) rises above normal levels. An increase of the number of smooth muscle cells in the walls of small lung arteries (a phenomenon called proliferation) that are remodeling the vessels, may lead to obstructions in the microcirculation, which will then lead to an increase in the blood pressure. Chronic thromboembolic pulmonary hypertension is a complication representing less than 1% of all cases of acute pulmonary embolism (the sudden blocking of a lung artery by a clot or foreign material which has been brought to its site by the blood current), which directly leads to pulmonary hypertension. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension are chronically debilitating and life-threatening

Pulmonary arterial hypertension (PAH) is still an important cause of morbidity and mortality in children. Despite recent developments in PAH-specific therapies, survival of patients with idiopathic PAH remains poor and appears to be worse in children compared with adults. During the past few years, treatment of PAH has undergone a remarkable evolution, which has led to the current approval by regulatory agencies of few drugs for adult patients from three main pharmacological groups (addressing three pathways) and four different routes ofadministration (oral, inhaled, subcutaneous andintravenous). In pediatric PAH, blood low exiting the right side of the heart faces great erresistance due to increased muscle present in the walls of the lungs. The right ventricle then enlarges and thickens in response, which may lead to heart failure. However, emerging therapeutic strategies for adult PAH, such as upfront oral combination therapy, have not been sufficiently studied in children[1]. Moreover, the complexity of pulmonary hypertensive vascular disease (PHVD) in children makes the selection of appropriate etherapies a great challenge far away from amere prescription of drugs. Therapy of pediatric PH is rather characterized by a complex strategy that includes the evaluation of severity and prognosis of the individual disease, the estimation of efficacy of different drugs, and their interaction and combination, as well as supportive and generalmeasures[1-2].

Recently, additional surgical and interventional techniques for palliation of children with severe PAH have been

reported. The beneficial effects ofthese strategies are mainly based on the relief of right ventricle (RV) pressure over load with a subsequent reduction of the interventricular septum shift to the left ventricle (LV), and improvement of systolic and diastolic LV performance. Although there is still a lack of data on effectiveness, formulation, pharmacokinetics, optimal dosing and treatment strategies, data are emerging that allow for the definition of appropriate treatment targets and goal-oriented therapy in children. Nevertheless, children with PAH are currently treated with targeted PAH drugs with benefit. Conservative treatments overview for PAH have been provided and established in many articles[1-14]. Here with provided an overview of recent updates advance treatments and available pharmaceutical dosage forms.

PHARMACOTHERAPY

Many medications have been used and studied in the treatment of pediatric PAH. However, there are three medication classes that have been evaluated more thoroughly for their efficacy in pediatric PH treatment: phosphodiesterasetype 5 (PDE5) inhibitors, endothelin (ET) receptor antagonists, and prostacyclinagonists. Other medications used are calcium channel blockers, anticoagulants, and inhaled nitric oxide (iNO). Prior to initiation of targeted PH therapy, thepatient should be assessed for acute vasodilator responsiveness via cardiac catheterization; left-sided heart disease or pulmonary venous disease resultingin an anatomic obstruction should be excluded. Medication therapy is determined based on patient responsiveness to acute vasodilator testing (AVT; Figure 1)[1]. Acute vasodilator testing is used to assess the response of the pulmonary vascular bed to pulmonary-specific vasodilators. In children with IPAH or isolated pulmonary hypertensive vascular disease, response to AVT is defined as a decrease in mPAP of at least 10 mmHg to <40 mmHg, with normal or increased cardiacoutput and a decrease in mPAP 20%; an increase or no change in cardiacindex; and a decrease or no change in pulmonary vascular resistance/systemicvascular resistance ratio[1-2].

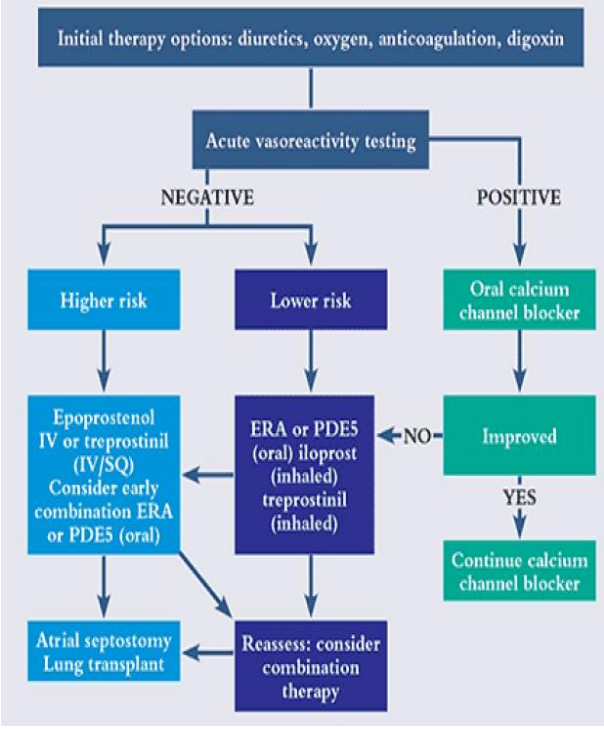

Figure 1- PAH: Pulmonary arterial hypertension; PDE5: Phosphdiesterase type 5; ERA: Endothelin receptor antagonist.

Conservative Treatment:

Therapies typically used for left heart failure have been alsoused for the treatment of patients with RV failure. Supportivetherapy may include oxygen, anticoagulants, diuretics, mineral corticoid receptor antagonists (spironolactone), digoxin. These measures are applied on an individual basis since the currently available studies provide either none or rather ambiguous/contradictory than valid data on most of these therapies in (adults and) children with PH[1-12].

CHEMISTRY OF PEDIATRIC PULMONARY ARTERIAL HYPERTENSION (PAH) DRUG

Endothelin-1 receptor antagonists

Bosentan:

It belongs to a class of highly substituted pyrimidine derivatives, with no chiral centers. It is designated chemically as 4-tert-butyl-N-[6-(2-hydroxy-ethoxy)-5-(2-methoxy-phenoxy)-[2,2′]-bipyrimidin4-yl]-benzenesulfonamidemonohydrate and has the following structural formula:

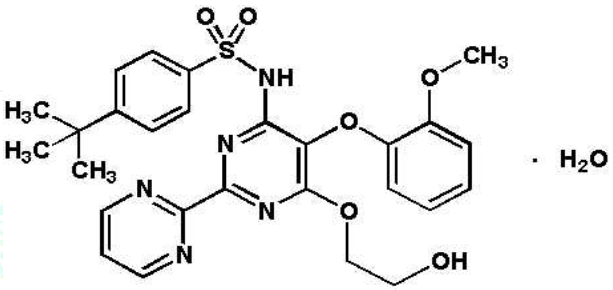

Figure 2 - Bosentan

Bosentan has a molecular weight of 569.64 and a molecular formula of $C_{27}H_{29}N_5O_6S \bullet H_2O$. Bosentan is a white to yellowish powder. 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). In the solid state, bosentan is very stable, is not hygroscopic and is not light sensitive[15].

Ambrisentan:

It is selective for the endothelin type-A (ETA) receptor. 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 a molecular weight of 378.42. It contains a single chiral center determined to be the (S) configuration and has the following structural formula:

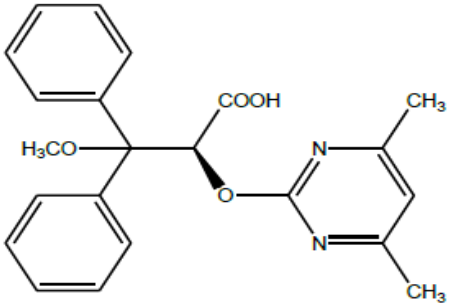

Figure 3 - Ambrisentan

Ambrisentan is a white to off-white, crystalline solid. It is a carboxylic acid with a pKa of 4.0. Ambrisentan is 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[16].

Macitentan:

The chemical name of macitentan is N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'propylsulfamide. It has a molecular formula of $C_{19}H_{20}Br_2N_6O_4S$ and a molecular weight of 588.27. Macitentan is achiral and has the following structural formula:

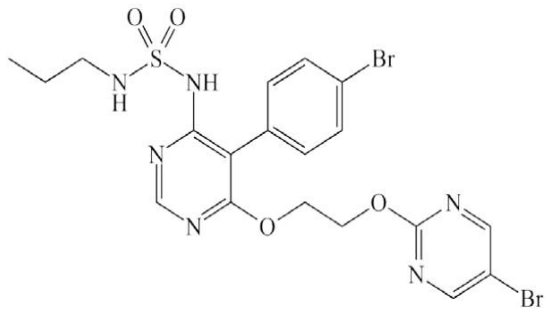

Figure 4 - Macitentan

Macitentan is a crystalline powder that is insoluble in water. In the solid state macitentan is very stable, is not hygroscopic, and is not light sensitive[17].

Phosphodiesterase Inhibitors (PDE-5i)

Sildenafil:

It is the citrate salt of sildenafil, a selective inhibitor of cyclic guanosine monophosphate(cGMP)-specific phosphor-diesterase type-5 (PDE-5). Sildenafil citrate is designated chemically as 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo [4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate and has the following structural formula:

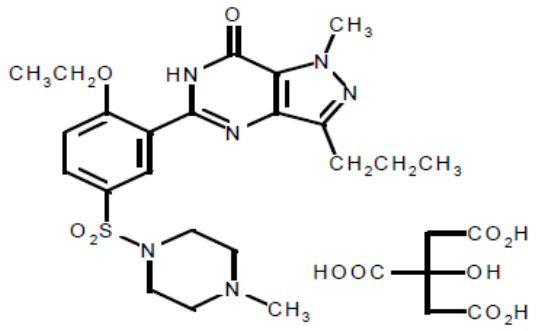

Figure 5 - Sildenafil citrate

Sildenafil citrate is a white to off-white crystalline powder with a solubility of 3.5 mg/mL in water. Sildenafil citrate has the empirical formula $C_{28}H_{38}N_6O_{11}S$ representing a molecular weight of 666.7[18].

Tadalafil:

It is an oral treatment for pulmonary arterial hypertension, is a selective inhibitor of cyclic guanosine monophosphate (cGMP)–specific phosphodiesterase type 5 (PDE5). Tadalafil has the empirical formula $C_{22}H_{19}N_3O_4$ representing a molecular weight of 389.41. The structural formula is:

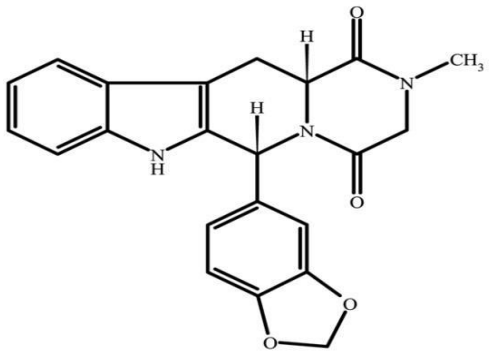

Figure 6 – Tadalafil

The chemical designation is pyrazino[1′,2′:1,6]pyrido[3,4–b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)2,3,6,7,12,12a-hexahydro-2-methyl-, (6R,12aR)-. It is a crystalline solid that is practically insoluble in water and very slightly soluble in ethanol[19].

Guanylate cyclase stimulators

Riociguat:

Riociguat is methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-lH-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamate with the following structural formula:

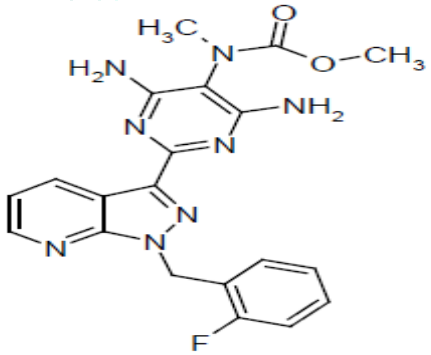

Figure 7 - Riociguat

Riociguat is a white to yellowish, crystalline, non-hygroscopic substance with a molecular weight of 422.42 g/mol. It has the empirical formula of $C_{20}H_{19}FN_8O_2$. In solid form it is stable to temperature, light, and humidity[20].

The solubility at 25°C in water: 4 mg/L, in ethanol: 800 mg/L, in 0.1 HCl (pH 1): 250 mg/L and in buffer (phosphate) pH.7: 3 mg/L. In the pH range of 2 to 4 the solubility showed strong pH-dependency. Solubility increases at lower pH values[20].

Vericiguat:

Vericiguat is Methyl (4,6-diamino-2-(5-fluoro-1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)pyrimidin-5-yl)carbamate with the following structural formula:

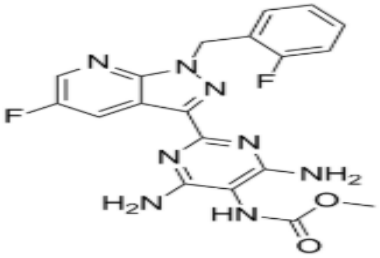

Figure 8 - Vericiguat

It has the empirical formula of $C_{19}H_{16}F_2N_8O_2$with a molecular weight of 426.388 g/mol. In solid form it is stable to temperature, light, and humidity[21,22].

Prostacyclin Analogues (Pca; Prostaglandin I Receptor Agonists; Ip Receptor Agonists)

Epoprostenol:

Epoprostenol (PGI2, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation.

Epoprostenol is (5*Z*,9a,11a,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprosta-5,13-dien-1-oic acid. Epoprostenol sodium has a molecular weight of 374.45 and a molecular formula of $C_{20}H_{31}NaO_5$. The structural formula is:

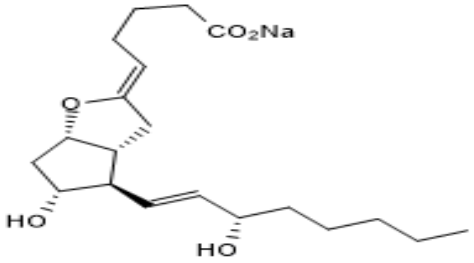

Figure 9 - Epoprostenol

Epoprostenol is a white to off-white lyophilized powder material. It is reconstituted with Sterile Water for Injection, USP, or Sodium Chloride 0.9% Injection, USP. The reconstituted solution of Epoprostenol has a pH ranging from 11 to 13 and is increasingly unstable at a lower pH[23].

Treprostinil:

Treprostinil is (1*R*,2*R*,3a*S*,9a*S*)-[[2,3,3a,4,9,9a-hexahydro-2-hydroxy-1-[(3*S*)-3-hydroxyoctyl]1*H*-benz[*f*]inden-5-yl]oxy]acetic acid. Treprostinil has a molecular weight of 390.52 and a molecular formula of $C_{23}H_{34}O_5$. The structural formula of treprostinil is:

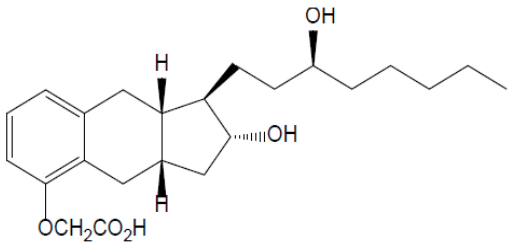

Figure 10 - Treprostinil

Treprostinil is chemically stable at room temperature and neutral pH. Sterile Diluent for Remodulin is a high-pH (pH~10.4) glycine diluent supplied in a 50 mL vial containing 50 mL of Sterile Diluent for Remodulin. Each vial contains 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (to adjust pH), and water for injection[24].

Iloprost:

The chemical name for iloprost is (*E*)-(3a*S*,4*R*,5*R*,6a*S*)-hexahydro-5-hydroxy-4-[(*E*)-(3*S*,4*RS*)-3- hydroxy-4-methyl-1-octen-6-ynyl]-Δ2(1*H*),Δ-pentalenevaleric acid. Iloprost consists of a mixture of the 4R and 4S diastereomers at a ratio of approximately 53:47. The molecular formula of iloprost is C22H32O4. Its relative molecular weight is 360.49. The structural formula is shown below:

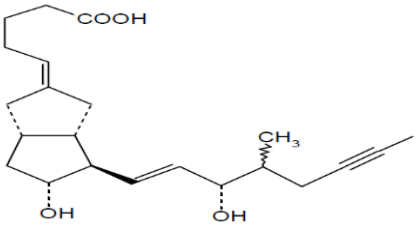

Figure 11 - Iloprost

Iloprost is an oily substance, which is soluble in methanol, ethanol, ethyl acetate, acetone and pH 7 buffer, sparingly soluble in buffer pH 9, and very slightly soluble in distilled water, buffer pH 3, and buffer pH 5[25].

Beraprost:

Beraprost is sodium 4-{(1R,2R,3aS,8bS)-2-Hydroxy-1-[(1E,3S)-3-hydroxy-4-methyl-1-octen-6-yn-1-yl]-2,3,3a,8b-tetrahydro-1H-benzo[b]cyclopenta[d]furan-5-yl}butanoic acid.

The Structural formula of beraprostis:

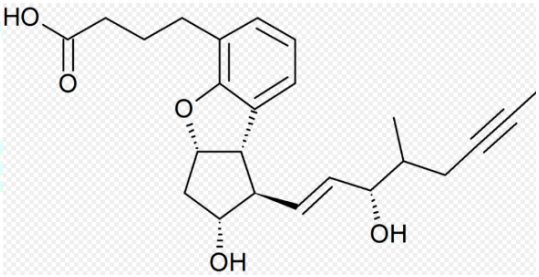

Figure 12 – Beraprost

Beraprost has a molecular weight of 398.492 and a molecular formula of $C_{24}H_{30}O_5$. It is chemically stable at room temperature and neutral pH[26,27].

Selexipag:

UPTRAVI (selexipag) is a selective non-prostanoid IP prostacyclin receptor agonist. The chemical name of selexipag is 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N(methylsulfonyl) acetamide. It has a molecular formula of $C_{26}H_{32}N_4O_4S$ and a molecular weight of 496.62. Selexipag has the following structural formula:

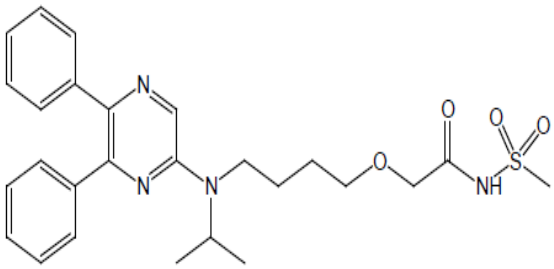

Figure 13 -Selexipag

Selexipag is a pale yellow crystalline powder that is practically insoluble in water. In the solid state selexipag is very stable, is not hygroscopic, and is not light sensitive[28].

TREATMENT ALGORITHM FOR PEDIATRIC PULMONARY ARTERIAL HYPERTENSION (PAH)

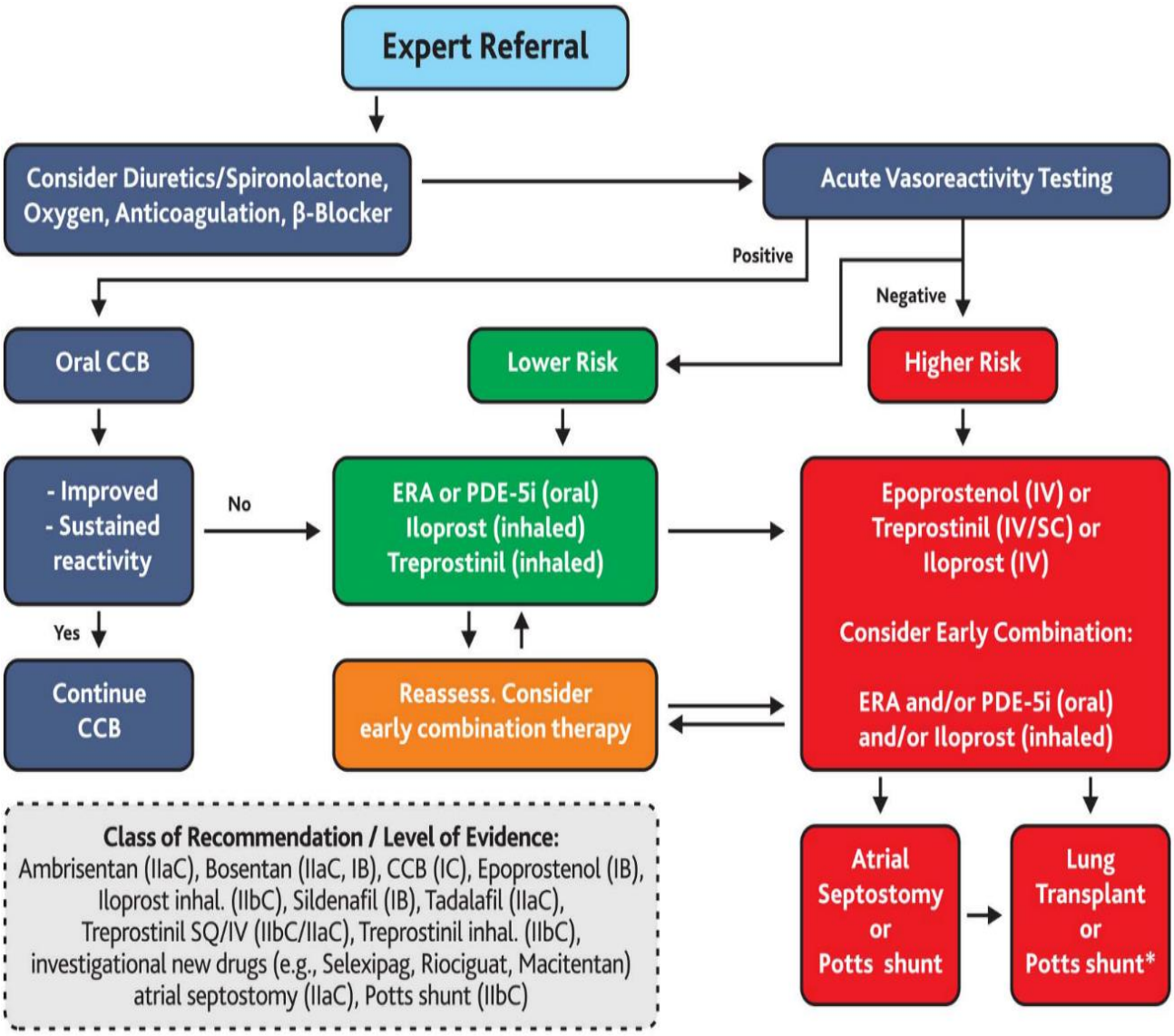

Figure 14 -Treatment algorithm for pediatric pulmonary arterial hypertension (PAH)[2].

DOSAGE FORM AND MECHANISAM OF PEDIATRIC PULMONARY ARTERIAL HYPERTENSION (PAH) DRUG:

Table 1 - Endothelin-1 receptor antagonists

Drug Name	Brand name	Dosage form	Excipients used	Mechanism of action
Endothelin-1 receptor antagonists				
Bosentan[15]	TRACLEER® (bosentan) tablets	Immediate release tablets	Bosentan is available as 62.5 mg and 125 mg film-coated tablets for oral administration, and contains the following excipients: corn starch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropylmethylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, and ethylcellulose. Each Tracleer 62.5 mg tablet contains 64.54 mg of bosentan monohydrate, equivalent to 62.5 mg of anhydrous bosentan. Each Tracleer 125 mg tablet contains 129.08 mg of bosentan monohydrate, equivalent to 125 mg of anhydrous bosentan.	Bosentan is a specific and competitive antagonist at endothelin receptor types ETA and ETB. Bosentan has a slightly higher affinity for ETA receptors than for ETB receptors. The clinical impact of dual endothelin blockage isunknown. Endothelin-1 (ET-1) is a neurohormone, the effects of which are mediated by binding to ETA and ETB receptors in the endothelium and vascular smooth muscle. ET-1 concentrations are elevated in plasma and lung tissue of patients with PAH, suggesting a pathogenic role for ET-1 in this disease.
	TRACLEER® (bosentan) tablets for oral suspension	Tablets for suspension	Bosentan is also available as a 32 mg tablet for oral suspension and contains the following excipients: cellulose microcrystalline, calcium hydrogen phosphate anhydrous, croscarmellose sodium, silica colloidal anhydrous, tartaric acid, tuttifrutti flavor, aspartame (E951), acesulfame potassium, and magnesium stearate. Each dispersible tablet contains 1.87 mg of phenylalanine. Each dispersible tablet contains 33.045 mg of bosentan monohydrate, equivalent to 32 mg anhydrous bosentan.	
Ambrisentan[16]	Letairis (ambrisentan) tablets	Immediate release tablets	Ambrisentan is available as 5 mg and 10 mg film-coated tablets for once daily oral administration. The tablets include the following inactive ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The tablets are film-coated with a coating material containing FD&C Red #40 aluminum lake, lecithin, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. Each square, pale pink Letairis tablet contains 5 mg of ambrisentan. Each oval, deep pink Letairis tablet contains 10 mg of ambrisentan.	Endothelin-1 (ET-1) is a potent autocrine and paracrine peptide. Two receptor subtypes, ETA and ETB, mediate the effects of ET-1 in the vascular smooth muscle and endothelium. The primary actions of ETA are vasoconstriction and cell proliferation, while the predominant actions of ETB arevasodilation, antiproliferation, and ET-1 clearance. In patients with PAH, plasma ET-1 concentrations are increased as much as 10-fold and correlate. with increased mean right atrial pressure and disease severity. ET-1 and ET-1 mRNA concentrations are increased as much as 9-fold in the lung tissue of patients with PAH, primarily in the endothelium of pulmonary arteries. These findings suggest that ET-1 may play a critical role in the pathogenesis and progression of PAH. Ambrisentan is a high-affinity (Ki=0.011 nM) ETA receptor antagonist with a high selectivity for the ETA versus ETB receptor (>4000-fold). The clinical impact of high selectivity for ETA is not known.

Macitentan [17]	OPSUMIT (macitentan) tablets	Immediate release tablets	OPSUMIT is available as a 10 mg film-coated tablet for once daily oral administration. The tablets include the following inactive ingredients: lactose monohydrate, magnesium stearate, micro-crystalline cellulose, polysorbate 80, povidone, and sodium starch glycolate Type A. The tablets are film-coated with a coating material containing polyvinyl alcohol, soya lecithin, talc, titanium dioxide, and xanthan gum.	Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of deleterious effects, such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage. Macitentan is an endothelin receptor antagonist that prevents the binding of ET-1 to both ETA and ETB receptors. Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. One of the metabolites of macitentan is also pharmacologically active at the ET receptors and is estimated to be about 20% as potent as the parent drug in vitro.

Table 2 - Phosphodiesterase inhibitors (PDE-5i)

Drug Name	Brand name	Dosage form	Excipients used	Mechanism of action
Phosphodiesterase inhibitors (PDE-5i)				
Sildenafil[18]	REVATIO (sildenafil) tablets	Immediate release tablets	REVATIO is formulated as white, film-coated round tablets with 20 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate, and triacetin.	Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE-5) in the smooth muscle of the pulmonary vasculature, where PDE-5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with PAH, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation. Studies in vitro have shown that sildenafil is selective for PDE-5. Its effect is more potent on PDE-5 than on other known phosphodiesterases (10-fold for PDE6, greater than 80-fold for PDE1, greater than 700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately 4,000-fold selectivity for PDE-5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE-5 compared to PDE6, an enzyme found in the retina and involved in the photo transduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels. In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE-5 is also found in other tissues including vascular and visceral smooth muscle and in
	REVATIO (sildenafil) for oral suspension	Powder for oral suspension	REVATIO is supplied in an amber glass bottle as a white to off-white powder providing a white to off-white grape flavored oral suspension when constituted. Bottles containing 32.27 g powder for oral suspension are intended for constitution with 90 mL water to produce an oral suspension containing 10 mg/mL sildenafil. In addition to the bottle, a press-in bottle adapter and an oral dosing syringe (2 mL) are provided. The inactive ingredients include sorbitol, citric acid anhydrous, sucralose, sodium citrate dihydrate, xanthan gum, titanium dioxide, sodium benzoate, colloidal silicon dioxide anhydrous and grape flavor	
	REVATIO (sildenafil) injection	Intravenous injection	REVATIO is supplied as a clear, colorless, sterile, ready to use solution containing 10 mg (12.5 mL) of sildenafil. Each mL of solution contains 1.124 mg sildenafil citrate, 50.5 mg	

			dextrose and water for injection.	platelets. The inhibition of PDE-5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of nitric oxide observed in vitro, and the mild peripheral arterial-venous dilatation in vivo.
Tadalafil[19]	ADCIRCA (tadalafil) tablets	Immediate release tablets	ADCIRCA is available as orange, film–coated, almond–shaped tablets for oral administration. Each tablet contains 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.	Tadalafil is an inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for the degradation of cyclic guanosine monophosphate (cGMP). Pulmonary arterial hypertension is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations in the pulmonary vascular s mooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of pulmonary vascular smooth muscle cells and vasodilation of the pulmonary vascular bed. Studies in vitro have demonstrated that tadalafil is a selective inhibitor of PDE5. PDE5 is found in pulmonary vascular smooth muscle, visceral smooth muscle, corpus cavernosum, skeletal muscle, platelets, kidney, lung, cerebellum, and pancreas.

Table 3 - Guanylate cyclase stimulators

Drug Name	Brand name	Dosage form	Excipients used	Mechanisum of action
Guanylate cyclase stimulators				
Riociguat[20]	Adempas (riociguat) tablets	Immediate release tablets	The inactive ingredients are cellulose microcrystalline, crospovidone, hypromellose 5cP, lactose monohydrate, magnesium stearate, sodium laurylsulfate, hydroxypropylcellulose, hypromellose 3cP, propylene glycol, titanium dioxide.	Riociguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitricoxide (NO). When NO binds to sGC, the enzyme catalyzes synthesis of the signaling molecule cyclic guanosine monophosphate (cGMP). Intracellular cGMP plays an important role in regulating processes that influence vascular tone, proliferation, fibrosis andinflammation. PAH is associated with endothelial dysfunction, impaired synthesis of nitric oxide and insufficient stimulation of the NO-sGC-cGMP pathway. Riociguat has a dual mode of action. It sensitizes sGC to endogenous NO by stabilizing the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO.Riociguat stimulates the NO-sGC-cGMP pathway and leads to increased generation of cGMP with subsequent vasodilation.The active metabolite (M1) of riociguat is 1/3 to 1/10 as potent as riociguat.

Table 4 - Prostacyclin analogues (PCA; prostaglandin I receptor agonists; IP receptor agonists)

Drug Name	Brand name	Dosage form	Excipients used	Mechanism of action
Prostacyclin analogues (PCA; prostaglandin I receptor agonists; IP receptor agonists)				
Epoprostenol[23]	VELETRI (epoprostenol) for Injection	Infusion, intravenous infusion	Epoprostenol sodium is the sodium salt of epoprostenol, formulated as a sterile lyophilized powder for intravenous (IV) administration. Each vial of VELETRI contains epoprostenol sodium equivalent to either 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 100 mg sucrose, and 50 mg arginine. Sodium hydroxide is added to adjust pH.	Epoprostenol has 2 major pharmacological actions: (1) direct vasodilation of pulmonary and systemic arterial vascular beds, and (2) inhibition of platelet aggregation.
Treprostinil[24]	REMODULIN® (treprostinil) Injection	Injection, for subcutaneous or intravenous	Sterile Diluent for Remodulin is a high-pH (pH~10.4) glycine diluent supplied in a 50 mL vial containing 50 mL of Sterile Diluent for Remodulin. Each vial contains 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (to adjust pH), and water for injection	The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation.
Iloprost[25]	Ventavis (iloprost) Solution	Inhalation Solution	Each mL of the aqueous solution contains 0.01 mg iloprost, 0.81 mg ethanol, 0.121 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.51 mg hydrochloric acid (for pH adjustment to 8.1) in water for injection. The solution contains no preservatives.	Iloprost is a synthetic analog of prostacyclin PGI2. Iloprost dilates systemic and pulmonary arterial vascular beds. It also affects platelet aggregation but the relevance of this effect to the treatment of pulmonary hypertension is unknown. The two diastereoisomers of iloprost differ in their potency in dilating blood vessels, with the 4S isomer substantially more potent than the 4R isomer.
Selexipag[28]	UPTRAVI® (selexipag) tablets.	Immediate release tablets	The tablets include the following inactive ingredients:D-mannitol, corn starch, low substituted HPC, HPMC, and magnesium stearate. The tablets are film coated with a coating material containing hypromellose, propylene glycol, titanium dioxide, carnauba wax along with mixtures of iron oxide red, iron oxide yellow or iron oxide black.	Selexipag is an oral prostacyclin receptor (IP receptor) agonist that is structurally distinct from prostacyclin. Selexipag is hydrolyzed by carboxylesterase 1 to yield its active metabolite, which is approximately 37-fold as potent as selexipag. Selexipag and the active metabolite are selective for the IP receptor versus other prostanoid receptors (EP1-4, DP, FP, and TP).

PHARMACOKINETICS OF PEDIATRIC PULMONARY ARTERIAL HYPERTENSION (PAH) DRUG:

Table 5 – ADME of Bosentan

Drug Name	Absorption	Distribution	Metabolism	Elimination
Bosentan[15]	The absolute bioavailability of bosentan in normal volunteers is about 50% and is unaffected by food.	After oral administration, maximum plasma concentrations of bosentan are attained within 3–5 hours and the terminal elimination half-life is about 5 hours in healthy adult subjects. The exposure to bosentan after intravenous and oral administration is about twice as high in adult patients with PAH as it is in healthy adult subjects.	Bosentan has three metabolites, one of which is pharmacologically active and may contribute 10%–20% of the effect of bosentan. Bosentan is an inducer of CYP2C9 and CYP3A and possibly also of CYP2C19.	Bosentan is eliminated by biliary excretion following metabolism in the liver. Less than 3% of an administered oral dose is recovered in urine. Total clearance after a single intravenous dose is about 4 L/h in patients with PAH.

Table 6 – ADME of Ambrisentan

Drug Name	Absorption	Distribution	Metabolism	Elimination
Ambrisentan[29]	Ambrisentan was well absorbed following oral administration. It also showed high absolute oral bioavailability in preclinical species, indicating that it undergoes little or no first pass metabolism.	In vitro results showed that ambrisentan binds to plasma proteins to a higher extent in humans (98.9%) than in preclinical species (91.8-97.2%). In human serum, it was apparent that albumin was the primary binding protein in human plasma. The results of a rat tissue distribution study with [14C]-ambrisentan indicated a wide distribution of drug into tissues but elimination occurred relatively rapidly.	Metabolism data obtained following administration of [14C]-ambrisentan showed that metabolic pathways for ambrisentan were qualitatively similar in various species. The metabolites identified include 4,6 dimethyl-2-hydroxypryimidine, ambrisentan glucuronide, hydroxylatedambrisentan, O-demethylatedambrisentan, dihydroxylatedambrisentan, dihydroxylatedambrisentan glucuronide, hydroxylated ambrisentan glucuronide, and Odemethylhydroxymethyl ambrisentan.	Based on disposition studies conducted with [14C]-ambrisentan, it was apparent that the primary route of excretion of drug-related material was faeces in all preclinical species as well as in humans. In 12/44 humans, about 66% of the dose was recovered in faeces and in animal species, the faecal recovery generally accounted for 69%-91% of the dose. Urinary excretion was a minor route of elimination in both animal species (7-23%) as well as in humans (23%).

Table 7 – ADME of Macitentan

Drug Name	Absorption	Distribution	Metabolism	Elimination
Macitentan[30]	The absolute bioavailability of macitentan could not be established, as the development of an i.v. formulation was not technically feasible. Maximum plasma concentrations of macitentan are achieved about 8 hours after administration.	Macitentan and ACT-132577 are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50L and 40L for macitentan and ACT-132577, respectively. Macitentan and its active metabolite are highly bound to plasma proteins (>99%), primarily to albumin.	Macitentan undergoes biotransformation by hydroxylation, with CYP3A4 isoenzyme as the major contributor. The main metabolite is ACT-132577 (active M6), present at approximately 71% of total drug exposure in plasma. No particularly relevant consequences of polymorphism in CYP3A4 are expected.	The major excretion route of macitentan in humans, in the form of metabolites, is via urine, accounting for about 50% of the dose, while approximately 24% of the administered dose was recovered in faeces. Neither unchanged macitentan nor the active metabolite ACT-132577 were recovered in urine.

Table 8 – ADME of Sildenafil

Drug Name	Absorption	Distribution	Metabolism	Elimination
Sildenafil[18]	REVATIO is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (25-63%). Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state.	The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations. Bioequivalence was established between the 20 mg tablet and the 10 mg/mL oral suspension when administered as a 20 mg single oral dose of sildenafil (as citrate).	Sildenafil is cleared predominantly by the CYP3A (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE-5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects.	After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose). REVATIO Injection: The pharmacokinetic profile of REVATIO has been characterized following intravenous administration. A 10 mg dose of REVATIO Injection is predicted to provide a pharmacological effect of sildenafil and its N-desmethyl metabolite equivalent to that of a 20 mg oral dose.

Table 9 – ADME of Tadalafil

Drug Name	Absorption	Distribution	Metabolism	Elimination
Tadalafil[19]	After single oral-dose administration, the maximum observed plasma concentration (Cmax) of tadalafil is achieved between 2 and 8 hours (median time of 4 hours). Absolute bioavailability of tadalafil following oral dosing has not been determined.	The mean apparent volume of distribution following oral administration is approximately 77 L, indicating that tadalafil is distributed into tissues. At therapeutic concentrations, 94% of tadalafil in plasma is bound to proteins.	Tadalafil is predominantly metabolized by CYP3A to a catechol metabolite. The catechol metabolite undergoes extensive methylation and glucuronidation to form the methylcatechol and methylcatechol glucuronide conjugate, respectively. The major circulating metabolite is the methylcatechol glucuronide.	Following 40 mg, the mean oral clearance for tadalafil is 3.4 L/hr and the mean terminal half-life is 15 hours in healthy subjects. In patients with pulmonary hypertension not receiving concomitant bosentan, the mean oral clearance for tadalafil is 1.6 L/hr, and the mean terminal half-life is 35 hours. .

Table 10 – ADME of Riociguat

Drug Name	Absorption	Distribution	Metabolism	Elimination
Riociguat[20]	The absolute bioavailability of riociguat is about 94%. Peak plasma riociguat concentrations were observed within 1.5 hours after tablet intake. Food does not affect the bioavailability of riociguat.	The volume of distribution at steady state is approximately 30 L. Plasma protein binding in humans is approximately 95%, with serum albumin and α1–acidic glycoprotein being the main binding components. Riociguat is a substrate of P-gp and BCRP.	Riociguat is mainly cleared by metabolism by CYP1A1, CYP3A, CYP2C8 and CYP2J2. Formation of the major active metabolite, M1, is catalyzed by CYP1A1, which is inducible by polycyclic aromatic hydrocarbons such as those present in cigarette smoke. M1 is further metabolized to the inactive N-glucuronide. Plasma concentrations of M1 in patients with PAH are about half those for riociguat	Following oral administration of radiolabeled riociguat in healthy individuals, about 40 and 53% of the total radioactivity was recovered in urine and feces, respectively. There appears to be considerable variability in the proportion of metabolites and unchanged riociguat excreted, but metabolites were the major components of the dose excreted in most individuals.

Table 11 – ADME of Epoprostenol

Drug Name	Absorption	Distribution	Metabolism	Elimination
Epoprostenol[23]	The in vitro half-life of epoprostenol in human blood at 37°C and pH 7.4 is approximately 6 minutes; therefore, the in vivo half-life of epoprostenol in humans is expected to be no greater than 6 minutes.	Animal studies using tritium-labeled epoprostenol have indicated a high clearance (93 mL/kg/min), small volume of distribution (357 mL/kg), and a short half-life (2.7 minutes). During infusions in animals, steady-state plasma concentrations of tritium-labeled epoprostenol were reached within 15 minutes and were proportional to infusion rates.	Tritium-labeled epoprostenol has been administered to humans in order to identify the metabolic products of epoprostenol. Epoprostenol is metabolized to 2 primary metabolites: 6keto-PGF1α (formed by spontaneous degradation) and 6,15-diketo-13,14-dihydro-PGF1α (enzymatically formed), both of which have pharmacological activity orders of magnitude less than epoprostenol in animal test systems	The recovery of radioactivity in urine and feces over a 1-week period was 82% and 4% of the administered dose, respectively. Fourteen additional minor metabolites have been isolated from urine, indicating that epoprostenol is extensively metabolized in humans.

Table 12 – ADME of Trepostinil

Drug Name	Absorption	Distribution	Metabolism	Elimination
Trepostinil[24]	Trepostinil is relatively rapidly and completely absorbed after subcutaneous infusion, with an absolute bioavailability approximating 100%. Steady-state concentrations occurred in approximately 10 hours. Concentrations in patients treated with an average dose of 9.3 ng/kg/min were approximately 2,000 ng/L.	The volume of distribution of the drug in the central compartment is approximately 14 L/70 kg ideal body weight. Remodulin at in vitro concentrations well above what is clinically relevant was 91% bound to human plasma protein.	Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. In a study conducted in healthy volunteers using [14C] treprostinil, 79% and 13% of the subcutaneous dose was recovered in the urine and feces, respectively, over 10 days. Only 4% was excreted as unchanged treprostinil in the urine. Five metabolites were detected in the urine, ranging from 10% to 16% and representing 64% of the dose administered.	The elimination of treprostinil (following subcutaneous administration) is biphasic, with a terminal elimination half-life of approximately 4 hours using a two-compartment model. Systemic clearance is approximately 30 L/hour for a 70 kg person.

Table 13 – ADME of Iloprost

Drug Name	Absorption	Distribution	Metabolism	Elimination
Iloprost[25]	The absolute bioavailability of inhaled iloprost has not been determined.	Following intravenous infusion, the apparent steady-state volume of distribution was 0.7 to 0.8 L/kg in healthy subjects. Iloprost is approximately 60% protein-bound, mainly to albumin, and this ratio is concentration-independent in the range of 30 to 3000 pg/mL.	Clearance in normal subjects was approximately 20 mL/min/kg. Iloprost is metabolized principally via ß-oxidation of the carboxyl side chain. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form. In animal experiments, tetranor-iloprostwas pharmacologically inactive.	A mass-balance study using intravenously and orally administered [3H]-iloprost in healthy subjects (n=8) showed recovery of total radioactivity over 14 hours post-dose, was 81%, with 68% and 12% recoveries in urine and feces, respectively

Table 14 – ADME of Selexipag

Drug Name	Absorption	Distribution	Metabolism	Elimination
Selexipag[28]	The absolute bioavailability of selexipag is approximately 49%. Upon oral administration, maximum observed plasma concentrations of selexipag and its active metabolite are reached within about 1–3 hours and 3–4 hours, respectively.	The volume of distribution of selexipag at steady state is 11.7 L. Selexipag and its active metabolite are highly bound to plasma proteins (approximately 99% in total and to the same extent to albumin and alpha1-acid glycoprotein).	Selexipag is hydrolyzed to its active metabolite, (free carboxylic acid) in the liver and intestine by carboxylesterases. Oxidative metabolism, catalyzed mainly by CYP2C8 and to a smaller extent by CYP3A4, leads to the formation of hydroxylated and dealkylated products. UGT1A3 and UGT2B7 are involved in the glucuronidation of the active metabolite. Except for the active metabolite, none of the circulating metabolites in human plasma exceeds 3% of the total drug-related material.	Elimination of selexipag is predominately via metabolism with a mean terminal half-life of 0.8-2.5 hours. The terminal half-life of the active metabolite is 6.2-13.5 hours. There is minimal accumulation of the active metabolite upon twice daily repeat administration suggesting that the effective half-life is in the range of 3-4 hours.

CONCLUSION:

This systematic review accomplishes 3 important objectives:

(a) This underlines the need for effective therapies to treat the broad range of PH presentations in neonataland pediatric pulmonology, cardiology, and critical care.

(b) This intensely suggests that PDE5 inhibitors improve oxygenation and hemodynamic parameters in pediatric patients.

(c) This repeats the need for additional well-planned, prospective, comparative studies of the safety and efficacy of PDE inhibitors, other pulmonary vasodilators, and placebo controls in infants and children with PH[53].

In the relatively small number of children studied, the survival rate was better in those children given combination therapy with epoprostenol and bosentan, with or without sildenafil, than in those on monotherapy. The indication for additional therapy was either an unsatisfactory response to initial therapy (epoprostenol or bosentan) or clinical deterioration. The concept of starting treatment with a single agent, preferably an oral drug, followed by the addition of a different agent(s) if necessary is supported by the benefit shown in several adult studies. Initiation of treatment with combination therapy has not been formally evaluated.

Transdermal drug delivery systems have been used as safe and effective drug delivery devices since 1981. A lot of progress has been done in the field of Transdermal Patches. Due to large advantages of the Transdermal Drug Delivery System, this system interests a lot of researchers. Many new researches are going on in the present day to incorporate newer drugs via this system. Transdermal dosage forms may provide clinicians an opportunity to offer more therapeutic options to their patients to optimize their care[54].

Transdermal system for PAH treatment to the children is not established so far. Considering the fact of children's comfortability in order to intake solid and semisolid oral or intravenous injection, transdermal patch with PDE inhibitors would be a choice of dosage form for pediatric PAH. Hence more research should happened to establish transdermal patch with PDE inhibitors for pediatric PAH.

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