Drug Saf (2015) 38:419–435
DOI 10.1007/s40264-015-0275-y

REVIEW ARTICLE

Comparative Safety and Tolerability of Endothelin Receptor Antagonists in Pulmonary Arterial Hypertension

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Published online: 20 March 2015

Abstract Pulmonary arterial hypertension (PAH) is a condition that leads to progressive right heart failure and death unless recognized and treated early. Endothelin, a potent endogenous vasoconstrictor, has been identified as an important mediator of PAH. Endothelin receptor antagonists (ERAs) have been associated with an improvement in exercise capacity and time to clinical worsening in patients with Group 1 PAH, and three different ERAs are currently approved for use in this population: bosentan, ambrisentan, and macitentan. While all three ERAs are generally well-tolerated, they each have important adverse effects that need to be recognized and monitored. In particular, they may cause anemia, peripheral edema, and mild cardiac, respiratory, neurologic, and gastrointestinal adverse effects to varying degrees. Although bosentan increases a patient's risk of developing liver transaminitis, ambrisentan and macitentan do not appear to confer the same risk of hepatotoxicity at this time. Important drug–drug interactions, particularly involving other drugs metabolized via the cytochrome P450 pathway, are important to recognize when prescribing ERAs. In this review, we provide a brief overview of the current state of knowledge as it relates to the adverse effect profiles, tolerability, and drug–drug interactions of this class of medication as informed by the results of randomized clinical trials, drug surveillance programs, and regulatory agencies.

Key Points

Bosentan is associated with an increased risk of developing liver transaminitis that may necessitate treatment discontinuation; ambrisentan and macitentan currently appear to confer a significantly lower risk of hepatotoxicity.

Bosentan, ambrisentan, and macitentan are all associated with the development of peripheral edema that is usually mild; the incidence of peripheral edema on ambrisentan or macitentan is particularly increased in older patients.

Bosentan, ambrisentan, and macitentan are all associated with the development of anemia that is usually mild.

1 Introduction

Pulmonary arterial hypertension (PAH) is a chronic, progressive, and debilitating disease with an estimated prevalence of 15–52 cases per million [1, 2] and an estimated annual mortality rate of 15 % [3]. It is defined by a sustained elevation in the mean pulmonary artery pressure (mPAP) of ≥25 mmHg at rest in the absence of other causes of pulmonary hypertension, including left-heart disease, hypoxemic lung disease, pulmonary thromboembolic disease, and miscellaneous hematologic, systemic, or metabolic disorders. Although it is often idiopathic or heritable, PAH is also associated with connective tissue diseases (CTDs) such as systemic sclerosis, systemic lupus erythematosus, and rheumatoid arthritis; infections such as

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HIV and schistosomiasis; congenital heart disease (CHD), certain drugs and toxins, and portal hypertension (Table 1) [4]. Although symptoms may be non-specific early in the disease course, clinical worsening is marked by exertional dyspnea, fatigue, chest pain, and syncope. Symptoms are graded by the four World Health Organization (WHO) functional classes of PAH severity [5].

The pathogenesis of PAH involves a combination of changes at the level of the pulmonary arteriole. These changes include vasoconstriction, smooth muscle and endothelial cell proliferation, and intravascular thrombosis, and lead to increased pulmonary vascular resistance and, ultimately, right heart failure [6]. Central to this process is the dysregulation of endothelin (ET)-1, a peptide produced mainly by endothelial cells that acts on both the ET-A and ET-B receptors in the lung [7]. The ET-A receptors, found abundantly on pulmonary vascular smooth muscle cells, induce vasoconstriction. The ET-B receptors are mainly located on endothelial cells and release vasodilatory and anti-proliferative mediators [8]; however, they are also found to a lesser extent on pulmonary vascular smooth muscle cells, where they stimulate both vasoconstriction and hyperplasia [9]. Under physiologic conditions in the lung, the predominant effect of ET-1 is vasodilation via the ET-B receptors. In the setting of PAH, however, ET-1 instead induces potent vasoconstriction and cell proliferation [7]. The cause of this shift in ET-1 activity in PAH is not entirely clear, but may be related to the upregulation of the ET-B receptors on pulmonary vascular smooth muscle cells, the downregulation of the ET-B receptors on endothelial cells [7], or the abnormally high concentration of ET-1, which results from increased production of the peptide [10]. Both circulating and pulmonary concentrations of ET-1 correlate to disease severity and prognosis in PAH [11].

In the 1990s, animal studies emerged demonstrating that endothelin receptor antagonism could both prevent and significantly reduce the vasoconstrictive and mitogenic actions of ET-1 under the pathologic conditions of PAH. In rat models with hypoxia-induced pulmonary hypertension, ET-A and ET-B receptor blockade reduced the mPAP, decreased pulmonary arterial wall thickness, and attenuated right atrial and right ventricular (RV) enlargement [12]. In 2001, bosentan, a sulfonamide-based dual endothelin receptor antagonist (ERA) that competitively binds the ET-A receptor with 20 times more affinity than the ET-B receptor [13], was studied in two different randomized, double-blind, placebo-controlled trials for the treatment of WHO functional class III or IV PAH. After demonstrating that the drug significantly improved patients' Borg dyspnea index, WHO functional class, and cardiopulmonary hemodynamic parameters, and delayed clinical worsening of PAH [14, 15], bosentan was approved for the treatment of PAH in North America in 2001 and in Europe in 2002. Since then, three other ERAs have been developed and approved for the treatment of PAH: sitaxsentan, a selective ET-A receptor antagonist; ambrisentan, a propanoic acid-based selective ERA that competitively binds the ET-A receptor with 260 times more affinity than the ET-B receptor [13]; and macitentan, another sulfonamide-based dual ERA that entered the market in 2013. Sitaxsentan was withdrawn from the market in 2010 after reports of fatal drug-induced hepatotoxicity emerged [16]. The pharmacodynamics and

Table 1 Updated classification of pulmonary hypertension in adults (modified with permission from Simonneau et al. [4])

1. PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4. CTEPH
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

CTEPH chronic thromboembolic pulmonary hypertension, *PAH* pulmonary arterial hypertension, *PH* pulmonary hypertension

1′ is the accepted subclassification for two conditions

Table 2 The pharmacodynamics and pharmacokinetics of bosentan, ambrisentan, and macitentan [13, 17, 18]

Parameter	Bosentan	Ambrisentan	Macitentan
Absorption	50 % oral bioavailability; peak concentration in 3–5 h	80 % oral bioavailability; peak concentration in 2 h	Unknown oral bioavailability; peak concentration in 8 h
Distribution	98 % protein bound	99 % protein bound	>99 % protein bound
Metabolism	CYP3A4 and CYP2C9	Mainly glucoronidation via UGT isoenzymes; some oxidation via CYP3A and CYP2C19	CYP3A4 and CYP2C19
Active metabolite(s)	Yes	No	Yes
Excretion	Feces	Feces, urine	Feces, urine
Half-life	5–8 h	13.6–16.5 h	16 h

CYP cytochrome P450, *UGT* uridine-diphospho-glucuronosyltransferase

Table 3 Recommended initial therapy for World Health Organization functional class II, III, and IV pulmonary arterial hypertension (modified with permission from Galiè et al. [16])

Recommendation	WHO-FC II	WHO-FC III	WHO-FC IV
I	Ambrisentan	Ambrisentan	Epoprostenol IV
	Bosentan	Bosentan	
	Macitentan	Epoprostenol IV	
	Riociguat	Iloprost inhaled	
	Sildenafil	Macitentan	
	Tadalafil	Riociguat	
		Sildenafil	
		Tadalafil	
		Treprostinil SC, inhaled	
IIa		Iloprost IV	Ambrisentan, bosentan
		Treprostinil IV	Iloprost inhaled and IV
			Macitentan
			Riociguat
			Sildenafil, tadalafil
			Treprostinil SC, IV, inhaled
IIIb		Beraprost	Initial combination therapy
		Initial combination therapy	

FC functional class, *IV* intravenous, *SC* subcutaneous, *WHO* World Health Organization

pharmacokinetics of bosentan, ambrisentan, and macitentan are summarized in Table 2 [13, 17, 18].

Currently, bosentan, ambrisentan, and macitentan are all approved as treatment for patients with Group 1 PAH who are WHO functional class II, III, or IV, and are used in addition to primary therapy with diuretics, oxygen (when indicated), digoxin (in some centers), and anticoagulants (in patients with idiopathic, anorexigen, or heritable PAH) (Table 3) [19]. Both the prescribing physician's and patient's choice of ERA is influenced by the specific adverse effects, tolerability (inversely proportional to the frequency that adverse effects lead to drug discontinuation), and potential drug–drug interactions of each of these medications. This literature review aims to describe the adverse effects, tolerability, and drug–drug interactions of bosentan, ambrisentan, and macitentan in adult patients with PAH as they have been reported in blinded, randomized, controlled trials (RCTs) that have compared the ERA as monotherapy to either placebo or another form of PAH-specific therapy; the open-label extension studies of these RCTs; post-marketing surveillance reports; and published product monographs. All articles and reports included in this review are current as of 1 September 2014. The RCTs were identified via PubMed using the search terms "bosentan pulmonary hypertension randomized" OR "sitaxsentan pulmonary hypertension randomized" OR "ambrisentan pulmonary hypertension randomized" OR "macitentan pulmonary hypertension randomized." From these results, the authors selected only articles that were blinded RCTs that compared monotherapy bosentan, ambrisentan, or macitentan in adult (age over 16 years) patients with Group 1 PAH to either placebo or another form of PAH-specific therapy, and excluded all observational studies, reviews, meta-analyses, comments, editorials, and letters. Additional

articles were identified from a manual search of references from the articles retrieved and were included if they provided additional discussion points despite not meeting the original criteria for this review; where cited, the specific methods of these articles are described. The open-label extension studies of the RCTs that were included in this review were searched for specifically using PubMed. Post-marketing surveillance data for bosentan and ambrisentan were obtained either directly from the Tracleer Excellence, Letairis Education and Access Program (LEAP), and Post-Marketing Observational Surveillance Programme for Ambrisentan (VOLT) databases, or published reports that included this data. In total, the adverse effect and tolerability data for bosentan were obtained from seven RCTs, four open-label extension studies, and one post-marketing surveillance report; data for ambrisentan were obtained from three RCTs, one open-label extension study, and two post-marketing surveillance reports; and data for macitentan were obtained from the one RCT that has been published to date. All adverse effects and rates of drug discontinuation due to adverse effects that were reported in the RCTs, their open-label extension studies, and post-marketing surveillance reports were included in this review. Certain adverse effects were not reported consistently in all RCTs, open-label extension studies, and post-marketing surveillance reports, and therefore do not appear consistently in this review. Drug–drug interaction data for all three ERAs was obtained from product monographs published by Health Canada, the European Medicines Agency, and the US Food and Drug Administration (FDA). This review includes the drug–drug interactions that were felt to be most significant for patients with PAH.

2 Clinical Data

The adverse effect, tolerability, and drug–drug interaction data on bosentan, ambrisentan, and macitentan in PAH that were included in this review was obtained from RCTs, open-label extension studies, post-marketing surveillance reports, and product monographs that included patients with various etiologies of Group 1 PAH and co-morbidities. Therefore, comparing data between these sources must be done cautiously.

2.1 Bosentan

Channick et al. [14] published the first double-blind, placebo-controlled RCT of bosentan 125 mg twice daily as monotherapy for PAH in 2001. It concluded that bosentan improved the exercise capacity, cardiopulmonary hemodynamics, Borg dyspnea index, and WHO functional class of patients with PAH. Similar results were reported in subsequent RCTs. BREATHE (Bosentan Randomized Trial of Endothelin Antagonist Therapy)-1 was a double-blind, placebo-controlled RCT that compared bosentan 125 and 250 mg twice daily to placebo for PAH [15]. Sitbon et al. [20] published a long-term, open-label extension study of patients in the Channick et al. trial in 2003. It evaluated 29 patients with PAH who received bosentan for a mean exposure time of 15.3 months. SERAPH (Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension) was a 16-week, double-blind RCT that compared bosentan to sildenafil in the treatment of PAH [21]. Two RCTs have evaluated bosentan as treatment for a specific etiology of PAH: ASSET-1 was a 16-week, double-blind, placebo-controlled RCT of bosentan 125 mg twice daily for the treatment of PAH secondary to sickle cell disease [22]; BREATHE-5 was a 16-week, double-blind, placebo-controlled RCT of bosentan 125 mg twice daily for the treatment of PAH secondary to CHD with Eisenmenger physiology [23]. BREATHE-5 was followed by an open-label extension study of 37 patients treated for a mean of 24 weeks [24]. The endothelin antagonist trial in mildly symptomatic pulmonary arterial hypertension patients (EARLY) trial was a double-blind, placebo-controlled RCT that evaluated bosentan therapy in patients with PAH who were less symptomatic than those included in prior studies (WHO functional class II patients) [25]. The EARLY trial was followed by a 5-year, open-label extension study that was ultimately able to evaluate 173 PAH patients who were treated with bosentan for a mean duration of 43.3 months [26]. STRIDE (Sitaxsentan To Relieve ImpaireD Exercise)-2 was a double-blind, placebo-controlled RCT of sitaxsentan for the treatment of PAH that included an open-label bosentan treatment arm consisting of 60 patients [27]. This trial was followed by an open-label extension study, STRIDE-2X, in which 84 PAH patients treated with bosentan 125 mg twice daily were evaluated after 1 year of treatment [28]. The study characteristics and incidence of adverse events reported in each RCT are summarized in Table 4.

When bosentan entered the market between 2001 and 2002, the FDA-mandated Tracleer Access Program (TAP) was developed to provide prescribing physicians with risk-management strategies for patients treated with bosentan. At the same time, the Tracleer Excellence Post Marketing Surveillance (TRAX-PMS) database was launched under the European Medicines Agency, which has collected data on adverse effects associated with bosentan outside of the trial setting [29].

A review of the seven published RCTs of bosentan as monotherapy for PAH in adults, their open-label extension studies, and the TRAX-PMS post-marketing surveillance report on bosentan reveals that the drug's tolerability is most commonly limited by hepatotoxicity, followed by

Table 4 Incidence of adverse events (%) reported in randomized controlled trials of bosentan as monotherapy for pulmonary arterial hypertension in adults

RCT	Etiology of PAH	Duration of treatment	Concomitant PH medications	Number of patients	Bosentan dose regimen or comparison group	Liver transaminitis (AST, ALT> 3X ULN)	Peripheral edema or fluid retention	Anemia	Nasopharyngitis or sinus congestion	Cough	Dyspnea	Chest pain	Palpitations	Flushing	Syncope	Headache	Dizziness or vertigo	Diarrhea	Nausea or vomiting	Fatigue
Channick et al. (2001)[14]	IPAH, APAH (scleroderma)	12 weeks	None	21	125 mg BID	9.5														
				11	Placebo															
BREATHE-1 (2002)[15]	IPAH, APAH (CTD)	16 weeks	None	74	125 mg BID	4				5	3			9	8	19	12			
				70	250 mg BID	14				6	7			9	10	23	10			
				69	Placebo	3				12	10			4	6	19	19			
SERAPH (2005)[21]	IPAH, APAH (CTD)	16 weeks	None	12	125 mg BID	0	16.7	0		8.3										
				14	Sildenafil	0		0					7.1							
BREATHE-5 (2006)[23]	Eisenmenger syndrome	16 weeks	None	37	125 mg BID	3	19					8	11		3	14	8			
				17	Placebo	0	6					0	0		0	12	6			
STRIDE-2 (2006)[27]	IPAH, APAH (CTD, CHD)	18 weeks	None	60	125 mg BID	11	15		8.3							10	5		6.7	5
				62	Placebo	6	8.1		6.5							8.1	3.2		0	3.2
EARLY (2008)[25]	IPAH, APAH (CTD, anorexigen use, HIV, CHD) with WHO FC II	6 months	Sildenafil (15%)	93	125 mg BID	13	6		8	4		5			1.1	4	5	2	5	
			Sildenafil (16%)	92	Placebo	2	8		9	8		4			0	10	5	8	9	
ASSET-1 (2010)[22]	Sickle cell disease	16 weeks	None	6	125 mg BID	0		67.7												
				8	Placebo	0														

RCTs = randomized controlled trials; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; IPAH = idiopathic pulmonary arterial hypertension; APAH = associated pulmonary arterial hypertension; CTD = connective tissue disease; CHD = congenital heart disease; HIV = human immunodeficiency virus; mg = milligram; BID = bis in die.

several less frequent hematologic, neurologic, cardiovascular, respiratory, and gastrointestinal adverse effects.

2.2 Ambrisentan

In 2005, Galié et al. published the first phase II clinical trial of ambrisentan as monotherapy for PAH. The 12-week blinded study, in which patients were randomized to receive 1, 2.5, 5, or 10 mg once daily, was followed by a 12-week open-label extension period during which the dose could be adjusted [30]. Subsequently, two concurrent phase III, randomized, placebo-controlled trials were published: ARIES (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies)-1, which used treatment doses of 5 or 10 mg once daily, and ARIES-2, which used treatment doses of 2.5 or 5 mg once daily [31]. Both of these studies concluded that ambrisentan improved the exercise capacity, Borg dyspnea index, and B-type natriuretic peptide levels of patients with PAH. In addition, ARIES-1 also concluded that ambrisentan improved WHO functional class and ARIES-2 concluded that the drug improved time to clinical worsening. ARIES-E, the long-term, open-label extension study of ARIES-1 and -2, followed a total of 383 patients with PAH who were treated with ambrisentan 2.5, 5, or 10 mg once daily over a period of 2 years [32]. The study characteristics and incidence of adverse events reported in each RCT are summarized in Table 5.

Since ambrisentan was approved for the treatment of PAH in 2007, LEAP and VOLT have published long-term data on 10,927 American [33] and 998 European patients [34], respectively, who have been treated with ambrisentan.

A review of the three published RCTs of ambrisentan as monotherapy for PAH in adults, the one open-label extension study, and the two post-marketing surveillance reports on ambrisentan reveals that the drug's tolerability is most commonly limited by peripheral edema, followed by several less frequent respiratory, cardiovascular, gastrointestinal, neurologic, and hematologic effects.

2.3 Macitentan

Macitentan is the latest endothelin antagonist representing an effort to enhance the efficacy and safety of ERAs. The SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome) trial is to date the only published RCT of macitentan for the treatment of PAH [35]. A total of 742

Table 5 Incidence of adverse events (%) reported in randomized controlled trials of ambrisentan as monotherapy for pulmonary arterial hypertension in adults

RCT	Etiology of PAH	Duration of treatment	Concomitant PH medications	Number of patients	Ambrisentan dose regimen or placebo	Liver transaminitis (AST, ALT> 3X ULN)	Peripheral edema or fluid retention	Nasopharyngitis	Nasal congestion	Sinusitis	Dyspnea	Palpitations	Flushing	Headache	Abdominal pain	Constipation
Galie et al. (2005)[30]	IPAH, APAH (CTD, HIV, anorexigen use)	12 weeks	None	16	1 mg OD	0										
				19	2.5 mg OD	0										
				16	5 mg OD	12.5										
				13	10 mg OD	0										
ARIES-1 (2008)[31]	IPAH, APAH (CTD, HIV, anorexigen use)	12 weeks	None	67	5 mg OD	0	26.9	7.5	6	4.5	6	0	3	17.9	3	4.5
				68	10 mg OD	0	28.4	3	10.4	4.5	4.5	4.5	1.5	19.4	3	6
				67	Placebo		10.4	1.5	3	0	3	3	0	20.9	1.5	1.5
ARIES-2 (2008)[31]	IPAH, APAH (CTD, HIV, anorexigen use)	12 weeks	None	64	2.5 mg OD	0	3.1	0	1.6	1.6	1.6	6.3	6.3	7.8	3.1	3.1
				63	5 mg OD	0	9.5	3.2	4.8	1.6	4.8	7.9	4.8	28.6	3.2	1.6
				65	Placebo		10.8	0	0	0	3.1	1.5	1.5	6.2	0	1.5

RCTs = randomized controlled trials; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal; IPAH = idiopathic pulmonary arterial hypertension; APAH = associated pulmonary arterial hypertension; CTD = connective tissue disease; HIV = human immunodeficiency virus; mg = milligram; OD = omni die.

patients with PAH were randomized to receive macitentan 3 mg once daily, 10 mg once daily, or placebo for a median treatment period of 115 weeks, during which time other PH therapies were permitted concomitantly. The study concluded that macitentan decreased morbidity and mortality in patients with PAH. The study characteristics and adverse events reported in this study are summarized in Table 6. SERAPHIN-OL, the long-term, open-label extension study, has yet to be completed and no post-marketing surveillance reports have been released since the drug was approved for treatment of PAH in 2013.

A review of the SERAPHIN trial reveals that the drug's tolerability in PAH patients is most commonly limited by nasopharyngitis and upper respiratory tract infection, followed by anemia and headache.

3 Hepatotoxicity

3.1 Bosentan

Hepatotoxicity is a well-described but incompletely understood adverse effect of bosentan. Bosentan is metabolized by cytochrome P450 (CYP) isoenzymes 2C9 and 3A4 in the liver and is excreted almost entirely into the bile [36]. The mechanism of bosentan-induced hepatotoxicity likely involves its modulation of various hepatobiliary transporters, the net effect of which can lead to the accumulation of cytotoxic bile acids. In in vitro studies using sandwich-cultured hepatocytes, bosentan has been shown to inhibit both the basolateral sodium-taurocholate cotransporting polypeptide (NTCP) and the organic anion-transporting polypeptides (OATPs) that are responsible for hepatic uptake of bile acids, as well as the bile salt export pump (BSEP) and the multidrug resistance-associated protein 2 (MRP2), which excrete bile acids into the bile canaliculi [37–39]. Interestingly, BSEP inhibition alone is related to the development of cholestatic liver disease, as seen in hereditary BSEP deficiency [40]. In addition to its effects on BSEP, recent evidence indicates that bosentan-induced hepatotoxicity may also be mediated more directly by its inhibition of the ET-B receptors on hepatocytes, an effect that induces portal sinusoid constriction [41].

Most of the RCTs of bosentan as monotherapy for PAH have reported elevated liver transaminases among the treatment groups. Among these seven studies, the incidence of liver transaminitis [defined as AST or ALT >3 times the upper limit of normal (ULN)] in the bosentan treatment groups varied between 0 and 14 % [14, 15, 21–23, 25, 27]. Six of these studies compared the incidence to a placebo group. In the BREATHE-5 trial, one patient (3 %) of the bosentan-treated group developed elevated liver enzymes greater than 5× ULN and was withdrawn from treatment. No patient in the placebo group developed liver transaminitis [23]. While the EARLY and STRIDE-2 trials reported an 11 and 5 % higher incidence in the

Table 6 Incidence of adverse events (%) reported in the randomized controlled trial of macitentan as monotherapy for pulmonary arterial hypertension in adults

RCT	Etiology of PAH	Duration of treatment	Concomitant PH medications	No. of patients	Macitentan dose regimen or placebo	Liver transaminitis (AST or ALT > 3× ULN)	Liver transaminitis (AST or ALT >3× ULN + bilirubin > 2× ULN)	Peripheral edema	Anemia
SERAPHIN (2013) [35]	IPAH, APAH (CTD, CHD, HIV, drug use, toxin use)	99.5 weeks	PDE-5 inhibitor (62.1 %) Oral/inhaled prostanoid (7.3 %)	250	3 mg od	3.6	2.1	16	8.8
		103.9 weeks	PDE-5 inhibitor (62 %) Oral/inhaled prostanoid (6.2 %)	242	10 mg od	3.4	1.7	18.2	13.2
		85.3 weeks	PDE-5 inhibitor (60.2 %) Oral/inhaled prostanoid (2.8 %)	249	Placebo	4.5	1.7	18.1	3.2

RCT	Hemoglobin <8 g/dL	Nasopharyngitis	Bronchitis	Upper respiratory tract infection	Cough	Dyspnea	Headache	Dizziness
SERAPHIN (2013) [35]	1.7	14.8	8	20	8	10.4	13.2	9.6
	4.3	14	11.6	15.3	8.7	7.4	13.6	10.7
	0.4	10.4	5.6	13.3	12	8.8	8.8	10.8

APAH associated pulmonary arterial hypertension, *CHD* congenital heart disease, *CTD* connective tissue disease, *IPAH* idiopathic pulmonary arterial hypertension, *od* once daily, *PAH* pulmonary arterial hypertension, *PDE-5* phosphodiesterase-5, *PH* pulmonary hypertension, *RCT* randomized controlled trial, *ULN* upper limit of normal

bosentan treatment groups than in the placebo groups, respectively [25, 27], the ASSET-1 trial reported no cases of elevated liver enzymes in either group [22]. While the BREATHE-1 trial also reported no significant difference in the incidence of elevated liver enzymes in the bosentan 125 mg twice daily group compared to the placebo group (4 vs. 3 %; $p = 1.00$), there was a significantly higher incidence in the bosentan 250 mg twice daily group (14 %; $p = 0.03$). In the 125 mg twice daily group, 3 % of patients developed elevated liver enzymes to 8× ULN ($p < 0.05$), as compared to 7 % of patients in the 250 mg twice daily group ($p < 0.1$). In aggregate, these data suggest that bosentan-mediated liver toxicity is likely dose related [15].

Of the patients who developed liver transaminitis on bosentan therapy, the Channick et al. [14, 23, 25, 27], BREATHE-5, EARLY, and STRIDE-2 trial data fortunately showed that it was invariably reversible with either no intervention, dose reduction, or drug discontinuation. No patients in the Channick et al. [14] trial, three patients in the BREATHE-1 trial [15], two patients in the STRIDE-2 trial [27], and one patient in the BREATHE-5 trial [23] discontinued treatment due to liver transaminitis.

The four open-label extension studies that followed patients who had participated in the RCTs have provided valuable information about bosentan-induced hepatotoxicity with long-term treatment. Sitbon et al. [20] reported that three out of 29 patients developed transient AST or ALT elevations above the ULN within 1 year of bosentan treatment, but none required treatment discontinuation. In the EARLY extension study, liver transaminitis was the most common cause of treatment discontinuation. In this 5-year study, 16.8 % of patients developed elevated liver enzymes, with 8.1 % of cases exceeding 8× ULN. The majority of cases occurred within the first 6 months of treatment. Of the 29 patients with elevated liver enzymes, 16 discontinued bosentan treatment. The Kaplan-Meier estimate of time to AST or ALT elevation (which corrected for shorter exposure time to bosentan for some patients) determined event rates of 12 % at year 1 (95 % CI 7.1–17.0) and 18.6 % by year 5 (95 % CI 12.3–24.9). Importantly, all cases of bosentan-induced liver transaminitis resolved either with no intervention, dose reduction, or drug discontinuation [26]. The BREATHE-5 extension study reported elevated liver enzymes in 5 % of treated patients. One case resolved with dose reduction and one resolved with drug discontinuation [24]. Data based on the evaluated population in the STRIDE-2X study revealed that the risk of developing elevated liver enzymes after 1 year of bosentan treatment was 14 % and the cumulative risk of discontinuing treatment after 1 year because of liver transaminitis was 9 % [28].

Table 7 Liver enzyme monitoring and treatment recommendations for the use of bosentan [43]

ALT/AST levels	Treatment and monitoring recommendations
1–3× ULN	Continue to monitor; no change in monitoring schedule or dose
>3 to < 5× ULN	Confirm by another test; if confirmed, reduce the dose or interrupt treatment and monitor LFT levels every 2 weeks
	Continue or reintroduce bosentan if levels return to pretreatment levels
>5 to <8× ULN	Confirm by another test; if confirmed, stop therapy; monitor LFTs at least every 2 weeks
	Consider reintroduction of therapy if LFTs return to pretreatment levels
>8× ULN	Stop therapy; do not reintroduce

LFT liver function test, *ULN* upper limit of normal

The results of 30 months of post-marketing surveillance via the TRAX-PMS database of 4,623 bosentan-naive patients treated for pulmonary hypertension in Europe were concordant with the published RCTs. Of the patients treated with bosentan, 7.6 % developed elevated aminotransferases (also defined as AST or ALT >3× ULN), corresponding to an annual rate of 10.1 %. The severity of liver enzyme elevation was most commonly between 3 and 5× ULN, and there were no cases of permanent or fatal liver injury associated with bosentan use. Liver transaminitis necessitated permanent discontinuation of the drug in only 3.2 % of patients. Subgroup analyses indicated little variation in the incidence of bosentan-induced liver injury among the various etiologies of PAH. There was, however, an even greater incidence in patients with PAH associated with CTD, but a lower incidence in patients with PAH secondary to CHD. The concomitant use of sildenafil and prostenoids did not increase the risk of developing liver transaminitis but ten patients who were anticoagulated while receiving bosentan treatment did develop serious liver injury (defined as ALT/ALT >3× ULN and total bilirubin >3× ULN or jaundice, in the absence of biliary obstruction) [42].

The findings from the TRAX-PMS database informed Actelion Pharmaceuticals' current recommendations for monthly AST and ALT monitoring for patients receiving bosentan treatment (Table 7) [43]. To date, no genetic or phenotypic markers have been identified as risk factors for the development of bosentan-induced hepatotoxicity. A case-control study comparing the polymorphisms in the genes encoding OATP, CYP2C9, and BSEP (*CYP2C9*, *SLCO1B1*, *SLCO1B3*, and *ABCB11*) in PAH patients with and without bosentan-related hepatotoxicity failed to show any significant associations [44].

Mild reductions in liver function do not appear to have an impact on bosentan metabolism or clearance [45]. However, more severe liver dysfunction may affect drug clearance. Recently, a retrospective evaluation of patients with portopulmonary hypertension treated with bosentan demonstrated that plasma concentrations of bosentan were higher in patients with Child-Pugh class B cirrhosis than in patients with PAH. However, the annual rate of bosentan-induced liver transaminitis in this population was not significantly higher than in the PAH population [46]. In the absence of larger studies to confirm bosentan's safety, both moderate and severe liver dysfunction are considered contraindications to its use [43].

3.2 Ambrisentan

Ambrisentan confers a relatively low risk of hepatotoxicity. This may be explained by the fact that unlike bosentan and macitentan, ambrisentan has very little effect on bile transport: in vitro, ambrisentan demonstrated weak inhibition of the NTCP and OATP transporters and virtually no inhibition of the BSEP [39]. This distinction may be because of its particular chemical structure, lack of affinity for the ET-B receptor, or its specific hepatic clearance. It is metabolized by glucuronidation via the uridine 5′-diphosphate glucuronosyltransferases and to a lesser extent by oxidation via CYP3A and CYP2C19 before it is excreted almost entirely into the bile [47].

In the study by Galié et al. only four patients out of a total of 64 receiving ambrisentan developed liver transaminitis over 24 weeks of treatment. Two patients in the 2.5 mg once daily group had elevated liver enzymes >3× ULN on one occasion but they subsequently normalized on repeat testing. Neither patient required dose reduction or treatment discontinuation. Two patients in the 5 mg once daily group developed more significant liver transaminitis: one patient's liver enzymes exceeded 8× ULN but normalized with the discontinuation of the drug, and another patient's liver enzymes exceeded 3× ULN and required drug discontinuation at 28 weeks. Considering that no patient in the 10 mg once daily group developed liver transaminitis, hepatotoxicity does not appear to be a dose-related effect [30].

ARIES-1 and ARIES-2 did not report any cases of elevated liver transaminases in any of the four treatment groups, while the combined incidence in the placebo groups was 2.3 % [31]. However, 12 patients who had been treated with ambrisentan had developed liver transaminitis during the 2-year follow-up period [32]. Ten of these patients had AST/ALT elevations between 3 and 5 × ULN and two patients had AST/ALT elevations >8× ULN. This corresponded to an estimated risk of developing liver transaminitis of 1.8 % (95 % CI 0.8–3.9) during the first

year of treatment, 3.9 % (95 % CI 2.2–6.8) in 2 years of treatment, and an overall annualized risk of 2 %. Liver transaminitis necessitated treatment discontinuation in two patients over the course of 2 years.

Ambrisentan may be a safe substitution for patients in whom bosentan-induced transaminitis does arise. An open-label, phase II study of ambrisentan for the treatment of 36 patients with PAH who had discontinued either bosentan or sitaxsentan (after a median of 9 weeks) due to liver transaminitis reported no cases of elevated aminotransferase levels (AST or ALT >3× ULN) in 12 weeks of follow-up [48]. The patients received 2.5 mg once daily for 4 weeks followed by 5 mg once daily for 8 weeks. Only one patient developed a transient rise in aminotransferase levels (exceeding 3× ULN), which resolved with a temporary dose reduction, and no patient required ambrisentan discontinuation. Even with long-term treatment (mean exposure 102 weeks) and dose increases (to 10 mg once daily in more than half of patients), no additional cases of liver transaminitis with ambrisentan were noted. In this study, 69.4 % of patients received concomitant prostanoid and/or sildenafil therapy.

VOLT reported that 3 % of treated patients (95 % CI 2.0–4.3) had recorded ALT and AST elevations >3× ULN at the same visit. This corresponded to an event rate per patient-year of 0.0140 (95 % CI 0.0094–0.0199) [34].

LEAP published a post-marketing surveillance report based on data from 10,927 American patients with PAH who were treated with ambrisentan for a mean of 330.5 days. A significant hepatic event (defined as either AST or ALT >3× ULN, total bilirubin >2× ULN, liver function test elevation with signs or symptoms of hepatic injury, or deemed medically serious by medical reviewers) occurred in only 0.72 % of patients [33].

Based on these data, in 2011 the US FDA deemed it no longer necessary to monitor liver enzymes monthly in patients taking ambrisentan; however, it is recommended that ambrisentan be discontinued if liver enzymes exceed 5× ULN, bilirubin exceeds 2× ULN, or there are signs of liver dysfunction in the absence of another cause [49].

3.3 Macitentan

Macitentan is metabolized in the liver by the CYP enzymes CYP3A4 and, to a lesser extent, CYP2C19 [18]. Unlike bosentan, macitentan does not appear to be hepatotoxic, despite their similar chemical structures and affinity for the ET-B receptor. In vitro, macitentan is even a more potent inhibitor of the NTCP, OATP, and BSEP than bosentan, possibly because it is more readily taken up by the hepatocyte [39]. It is therefore surprising and unclear why a higher incidence of liver transaminitis is not seen with macitentan therapy. One possibility may relate to the low dose of macitentan that is used to treat PAH, effectively limiting its hepatic accumulation [50].

The SERAPHIN trial reported that liver transaminitis did not develop more frequently in the treatment groups than in the placebo group. The incidence of liver transaminitis was 3.6 % in the macitentan 3 mg group, 3.4 % in the macitentan 10 mg group, and 4.5 % in the placebo group. However, elevations >8× ULN were fivefold greater on macitentan treatment (2.1 %) than with placebo (0.4 %) [35]. The hazard ratios for the first occurrence for ALT and/or AST elevation >3× ULN with macitentan 3 and 10 mg daily have been estimated to be 0.72 (95 % CI 0.30–1.74) and 0.64 (95 % CI 0.26–1.58), respectively. All cases of liver transaminitis were reversible with or without discontinuation of treatment [51].

Actelion Pharmaceuticals currently recommends monitoring liver enzymes prior to the initiation of macitentan and if clinically indicated during treatment. Treatment should be discontinued if sustained, clinically relevant aminotransferase elevations occur, if there is an increase in bilirubin >2× ULN, or in cases of symptoms of severe liver injury [52].

4 Peripheral Edema

The mechanism by which ERAs cause peripheral edema may be through their renal, cardiac, or vascular effects. It has long been postulated that ERAs cause fluid retention by blocking the natriuresis mediated by the ET-B receptors [53], and possibly also the ET-A receptors [54], in the renal collecting ducts. More recently, however, a study using RV myocardial samples from rats indicated that bosentan decreases the contractility of the hypertrophied RV by blocking what is presumably a compensatory upregulation of the ET-A receptor [55]. It is unclear to what extent this process occurs in PAH patients or if it is responsible for the peripheral edema. Although unsubstantiated, it is also possible that edema develops through the effect of ERAs on the capillary permeability [56].

4.1 Bosentan

Peripheral edema was a reported adverse effect of bosentan in four of the RCTs. In the SERAPH trial, the incidence of peripheral edema in patients treated with bosentan was 16.7 % (two patients), and it necessitated hospitalization for diuretic administration in both cases [21]. In the BREATHE-5 and STRIDE-2 trials, peripheral edema occurred 13 and 6.9 %, respectively; more commonly in the treatment group versus the placebo group [23, 27]. In the EARLY trial, however, peripheral edema developed in 2 %

fewer patients in the treatment group than in the placebo group [25].

The initial BREATHE-5 study and the BREATHE-5 extension study reported a 10 and 19 % incidence, respectively, of peripheral edema with long-term bosentan treatment [20, 24]. Peripheral edema led to treatment discontinuation in 3.6 % of patients in STRIDE-2X [28].

4.2 Ambrisentan

Peripheral edema is the most frequently reported adverse effect of ambrisentan. Galié et al. [30] reported an overall incidence of peripheral edema in 25 % of patients treated with ambrisentan 1, 2.5, 5, and 10 mg once daily within 12 weeks, with no significant differences among the treatment groups. In the ARIES-1 and ARIES-2 trials, the incidence of peripheral edema was not consistently higher in the treatment groups than in the placebo groups [32]. In the ARIES-1 trial, 17 % more patients developed peripheral edema in the combined treatment groups than in the placebo group. The incidence was 26.9, 28.4, and 10.4 % in the ambrisentan 5 mg once daily, 10 mg once daily, and placebo groups, respectively. In the ARIES-2 trial, however, 4.3 % fewer patients developed peripheral edema in the combined treatment groups than in the placebo group. The incidence was 3.1, 9.5, and 10.8 % in the 2.5 mg once daily, 5 mg once daily, and placebo groups, respectively.

Interestingly, a subgroup analysis indicated that ambrisentan may increase the risk of developing peripheral edema only in older patients. The incidence of peripheral edema among patients less than age 65 years in the treatment and placebo groups was not significantly different (14 vs. 13 %, respectively); however, 29 % of patients over the age of 65 years developed peripheral edema in the treatment group compared with 4 % in the placebo group [57]. Another post hoc analysis showed that patients who developed edema while taking ambrisentan still benefited from treatment. They had significantly increased exercise capacities, decreased Borg dyspnea indices, and improved WHO functional classes as compared with patients who developed edema while taking placebo [56].

Subsequently, as part of the 2-year follow-up of 383 patients receiving ambrisentan 2.5, 5, or 10 mg once daily, ARIES-E reported that peripheral edema continued to be a common adverse event, although the incidence has not been published. Most peripheral edema was noted to be mild (21 %) or moderate (16 %), but 1.3 % of patients experienced severe peripheral edema (one patient in the 2.5 mg once daily group, two patients in the 5 mg once daily group, and two patients in the 10 mg once daily group), and it resulted in drug discontinuation in one case [32].

The VOLT post-marketing surveillance data have indicated a 25 % incidence of peripheral edema in ambrisentan-treated patients [34].

4.3 Macitentan

The SERAPHIN trial reported that peripheral edema did not occur more frequently in either of the treatment groups compared with the placebo group [35]. The incidence of peripheral edema was 16 % in the macitentan 3 mg group, 18.2 % in the macitentan 10 mg group, and 18.1 % in the placebo group. However, more patients over the age of 65 years developed peripheral edema in the treatment groups than in the placebo group (30.3 % in the macitentan 3 mg group, 25.9 % in the macitentan 10 mg group, and 18.2 % in the placebo group) [51]. No patient required treatment discontinuation due to the development of peripheral edema.

5 Anemia

The mechanism by which anemia develops during ERA therapy is unclear, but it is thought to be in part dilutional as a result of the increased fluid retention [58]. It does not appear to be related to hemolysis or hemorrhage.

5.1 Bosentan

Although anemia was reported in many of the RCTs and open-label extension studies, it was generally mild, remained stable throughout treatment, and did not warrant treatment discontinuation. STRIDE-2 reported an overall decrease in the mean hemoglobin concentration of 0.5 g/dL from baseline to week 18 in the bosentan treatment group, which occurred within as early as 2 weeks of treatment. This was compared to a mean rise in hemoglobin concentration of 0.2 g/dL in the placebo group [27]. Sitbon et al. [20] reported hemoglobin concentration reductions in three patients, but never below 10.4 g/dL. The BREATHE-5 open-label extension study reported a marked decrease (<10 g/dL) in hemoglobin in only one patient (3 %) [24]. The EARLY extension study reported that 15 % of treated patients' hemoglobin concentrations dropped to <10 g/dL, necessitating transfusion in six patients and dose reduction in two patients [26].

Of note, bosentan-induced anemia may be more significant in patients with PAH secondary to sickle cell disease. The ASSET-1 trial reported that the decrease in hemoglobin was greater with bosentan than placebo. A greater than 15 % reduction in hemoglobin to an absolute value of <110 g/L occurred in 67 % of treated patients but never necessitated discontinuation of bosentan [22].

Actelion Pharmaceuticals currently recommends monitoring hemoglobin levels every 3 months for the duration of bosentan therapy [43].

5.2 Ambrisentan

Like bosentan, ambrisentan is also associated with a reduction in hemoglobin concentration that is mild and remains stable during treatment. Galié et al. [30] reported an overall mean reduction in hemoglobin concentration in all dose groups combined of 0.8 g/dL at week 12 of treatment. It did not decrease further during the subsequent 12 weeks of treatment. ARIES-1 and ARIES-2 reported that hemoglobin concentrations decreased from baseline to week 12 by a mean of 0.84 g/dL (±1.2 g/dL) in patients treated with ambrisentan, but the change was not dose dependent. This was compared with an overall increase in hemoglobin concentrations in the placebo group of 0.2 g/dL (±1.0 g/dL) by week 12 [31].

Data from the ARIES-E trial indicates that the reduction in hemoglobin concentration with ambrisentan therapy does stabilize over time. After 2 years of follow-up, the 2.5 and 5 mg once daily groups both had a mean hemoglobin concentration reduction of 1.1 g/dL, and the 10 mg once daily group had a mean hemoglobin concentration reduction of 1.2 g/dL [32].

The VOLT data indicated that 10 % of treated patients had a clinically significant decrease in hemoglobin and/or hematocrit at any visit during the program based on the investigator's judgement [34].

Considering that change in hemoglobin concentration is fairly stable over a 2-year treatment period, Gilead Sciences recommends that hemoglobin concentrations be measured only prior to initiation of ambrisentan, after 1 month of treatment, and periodically thereafter [57].

5.3 Macitentan

The SERAPHIN trial reported that the incidence of anemia was higher in the treatment groups than in the placebo group. The incidence in the 3 mg once daily, 10 mg once daily, and placebo groups was 8.8, 13.2, and 3.2 %, respectively, which reflects a dose-dependent effect of macitentan treatment [35]. The reduction in hemoglobin observed in the treatment groups stabilized after 4–12 weeks [51]. One patient in each treatment group discontinued treatment due to anemia. The anemia was reversible with treatment discontinuation [35].

Actelion Pharmaceuticals currently recommends measuring the hemoglobin concentration prior to initiating macitentan therapy and monitoring as clinically indicated during treatment [52].

6 Cardio-Respiratory Effects

6.1 Bosentan

Cough, dyspnea, nasopharyngitis, sinusitis, bronchitis, epistaxis, influenza-like illness, syncope, flushing, chest pain, and palpitations have all been reported with bosentan treatment in several RCTs. Cough was a reported adverse event in three of the RCTs. The incidence of cough varied between 4 and 8.3 % of bosentan-treated patients [15, 21, 25]. However, when compared with placebo in the BREATHE-1 and EARLY trials, bosentan treatment did not significantly increase the incidence of cough. The BREATHE-1 trial reported that cough occurred in 6 % of the combined treatment groups and 12 % of the placebo group ($p = 0.16$) [15], and in the EARLY trial cough occurred in 4 % of the treatment group and in 8 % of the placebo group [25]. In the SERAPH trial, one patient in the bosentan-treated group developed hemoptysis that resolved spontaneously [21].

Dyspnea was a reported adverse event only in the BREATHE-1 study. It occurred in 5 % of patients in the combined treatment groups, which was not significantly different than in the placebo group (10 %; $p = 0.15$) [15].

In the STRIDE-2 trial, nasopharyngitis or sinus congestion occurred more frequently in the treatment group than in the placebo group (8.3 vs. 6.5 %, respectively) [27], but not in the EARLY trial (8 % in the treatment group vs. 9 % in the placebo group) [25].

In three of the RCTs, syncope was reported in between 1.1 and 10 % of patients on bosentan treatment [15, 23, 25]. In the BREATHE-1 trial, there was no significant difference in the incidence of syncope in the bosentan treatment groups and the placebo group: it occurred in 9 % of the combined treatment groups and 6 % of the placebo group ($p = 0.59$), and it never led to treatment discontinuation [15]. In the BREATHE-5 trial, syncope occurred in 3 % of the treatment group but 0 % of the placebo group [23]. In the EARLY trial, syncope occurred in 1.1 % of the treatment group but 0 % of the placebo group [25].

Chest pain was a reported adverse event only in two of the RCTs, but it occurred more frequently in the treatment groups than the placebo groups in both [23, 25]. In the BREATHE-5 trial it occurred in 8 % of the treatment group and none of the placebo group [23], and in the EARLY trial it occurred in 5 % of the treatment group and 4 % of the placebo group [25]. One patient in the BREATHE-1 trial discontinued treatment due to angina pectoris [15].

Flushing was a reported adverse event in the BREATHE-1 trial only, and it did not occur in significantly more patients in the combined treatment groups than in the placebo group (9 vs. 4 %; $p = 0.28$) [15].

Palpitations were a reported adverse event in the BREATHE-5 trial only. The incidence was 11 % in the treatment group compared with 0 % in the placebo group [23].

The incidence of adverse cardiorespiratory events in patients treated with bosentan in the open-label extension studies was similar to the RCTs. The BREATHE-5 extension study reported that the incidence of both chest pain and nasopharyngitis was 11 % in treated patients, and the incidence of both palpitations and lower respiratory tract infection was 5 % in treated patients [24]. Sitbon et al. [20] also reported an incidence of upper respiratory tract infection in 31 %, dyspnea in 28 %, chest pain in 24 %, bronchitis in 21 %, palpitations in 21 %, cough in 14 %, influenza-like illness in 10 %, and epistaxis in 10 % of treated patients. The STRIDE-2X study reported that dyspnea led to drug discontinuation in 2.4 % of patients [28].

6.2 Ambrisentan

Galié et al. [30] reported that 18.8 % of patients treated with ambrisentan 1, 2.5, 5, and 10 mg once daily developed nasal congestion and upper respiratory tract infection within 12 weeks, with no significant difference among the treatment groups. In both the ARIES-1 and ARIES-2 trials, nasal congestion occurred more frequently in the treatment groups than in the placebo groups, and the effect was dose related. In the ARIES-1 trial, 5.2 % more patients in the combined treatment groups developed nasal congestion than in the placebo group. The incidence was 6, 10.4, and 3 in the 5 mg once daily, 10 mg once daily, and placebo group, respectively. In the ARIES-2 trial, 3.1 % more patients in the combined treatment groups developed nasal congestion than in the placebo group. The incidence was 1.6, 4.8, and 0 in the 2.5 mg once daily, 5 mg once daily, and placebo group, respectively [31]. Results were similar at the 2-year follow-up [32].

In both the ARIES-1 and ARIES-2 trials, sinusitis, nasopharyngitis, and dyspnea occurred more frequently in the treatment groups than the placebo groups, but the effect was not dose related. In the ARIES-1 trial, sinusitis occurred in 4.5 % more patients in the combined treatment groups than in the placebo group. In the ARIES-2 trial, it occurred in 1.6 % more patients in the combined treatment groups than in the placebo group. In the ARIES-1 trial, nasopharyngitis occurred in 3.7 % more patients in the combined treatment groups than in the placebo group. In the ARIES-2 trial, it occurred in 1.6 % more patients in the combined treatment groups than in the placebo groups. Dyspnea occurred in 2.2 % more patients in the combined treatment groups than in the placebo group in the ARIES-1 trial and in 0.05 % more patients in the combined treatment groups than in the placebo group in the ARIES-2 trial. Among the 261 patients receiving ambrisentan in both the ARIES-1 and -2 trials, one patient withdrew from treatment for worsening dyspnea, which may have been a symptom of worsening PAH [31]. At the 2-year follow-up, only 1.1 % of the 5 mg once daily group had withdrawn from treatment because of dyspnea [32].

The VOLT post-marketing surveillance data for ambrisentan has indicated a 15 % incidence of dyspnea and a 7 % incidence of cough in treated patients [34].

Galié et al. [30] reported that 12.5 % of patients treated with ambrisentan 1, 2.5, 5, and 10 mg once daily developed flushing within 12 weeks, with no significant difference between the treatment groups. In the ARIES-1 trial, flushing occurred in 2.2 % more patients in the combined treatment groups than in the placebo group. In the ARIES-2 trial, it occurred in 4 % more patients in the treatment groups than in the placebo group [31]. However, the effect was not dose related.

The incidence of palpitations in the treatment groups was not consistently higher than in the placebo groups in the ARIES-1 and ARIES-2 trials. Palpitations occurred in 0.8 % fewer patients in the combined treatment groups than in the placebo group in ARIES-1 but in 5.6 % more patients in the combined treatment groups than in the placebo group in ARIES-2 [31].

In the ARIES-E trial, only 2.1 % of the 2.5 mg once daily group had withdrawn from treatment due to syncope [32].

6.3 Macitentan

The SERAPHIN trial reported that upper respiratory tract infection and nasopharyngitis each occurred in 4 % more patients in the combined treatment groups than in the placebo group, but the effects were not dose related. The incidence of bronchitis was also 4 % higher in the combined treatment groups than in the placebo group, and the effect was dose related. The incidence of bronchitis was 8, 11.6, and 5.6 % in the macitentan 3 mg once daily, macitentan 10 mg once daily, and placebo groups, respectively. The incidence of dyspnea was only 0.14 % higher in the combined treatment groups than in the placebo group. Cough did not occur more frequently in either treatment group than in the placebo group. The incidence of cough was 8.4 % in the combined treatment groups and 12 % in the placebo group [35].

7 Neurological Effects

7.1 Bosentan

Headache and dizziness were reported adverse effects of bosentan in four of the RCTs. The incidence of headache varied between 4 and 23 % in the bosentan treatment groups

in each trial [15, 23, 25, 27]. In the BREATHE-1 trial, there was no significant difference in the incidence of headache in either the 125 or the 250 mg twice daily group compared with the placebo group. The incidence of headache in the 125 mg twice daily group and the placebo group was 19 % ($p = 1.00$) while the incidence in the 250 mg twice daily group was 23 % ($p = 0.68$) [15]. Similarly, in the EARLY trial, there was a 4 % incidence of headache in the bosentan-treated group compared with a 10 % incidence in the placebo group [25]. However, in both the BREATHE-5 and STRIDE-2 trials, the incidence of headache was 2 % higher in the treatment groups than in the placebo groups [23, 27]. The BREATHE-5 extension study and Sitbon et al. [20, 24] reported a 5 and 31 % incidence of headache, respectively, in patients treated with bosentan long-term.

The incidence of dizziness varied between 5 and 12 % in the bosentan treatment groups in each trial [15, 23, 25, 27]. In the BREATHE-1 trial, there was no significant difference in the incidence of dizziness in either the 125 or the 250 mg twice daily group compared with the placebo group. The incidence of dizziness was 19 % in the placebo group, 12 % in the 125 mg twice daily group ($p = 0.35$), and 10 % in the 250 mg twice daily group ($p = 0.15$) [15]. In the EARLY trial, dizziness was reported in the same amount of patients in the treatment and placebo groups [25]. In the BREATHE-5 and STRIDE-2 trials, the incidence of dizziness was nearly 2 % higher in the treatment groups than in the placebo groups [23, 27]. The BREATHE-5 extension study and Sitbon et al. [20, 24] reported a 5 and 17 % incidence of dizziness, respectively, in patients treated with bosentan long-term.

7.2 Ambrisentan

Galié et al. [30] reported an overall incidence of headache in 15.6 % of patients treated with ambrisentan 1, 2.5, 5, and 10 mg once daily by week 12, with no significant differences among the treatment groups. In the ARIES-1 and ARIES-2 trials, the incidence of headache was not consistently higher in the treatment groups than in the placebo groups. Headache occurred in 2.3 % fewer patients in the combined treatment groups than in the placebo group in the ARIES-1 trial, but 12 % more patients in the combined treatment groups than in the placebo group in the ARIES-2 trial [31]. One patient discontinued treatment because of headache. ARIES-E reported a similar frequency of headache after 2 years of treatment, although the incidence was not published [32].

The VOLT post-marketing surveillance data have indicated a 9 % incidence of headache and a 7 % incidence of dizziness in treated patients [34].

7.3 Macitentan

The SERAPHIN trial reported that headache occurred in 4.6 % more patients in the combined treatment groups than in the placebo group. The incidence of dizziness was 0.65 % less in the combined treatment groups than the placebo group [35].

8 Gastrointestinal Effects

8.1 Bosentan

Nausea has been reported with bosentan treatment in two of the RCTs, but the incidence was higher than in the placebo group in only one of the trials [25, 27]. In the EARLY trials, nausea occurred in 5 % of the treatment group, which was 4 % less frequent than in the placebo group [25]. In the STRIDE-2 study, nausea was reported in 6.7 % more patients in the treatment group than in the placebo group [27].

In the EARLY trial, diarrhea occurred in 2 % of the treatment group, which was 6 % less frequent than in the placebo group [25].

In the BREATHE-5 extension study, 8 % of patients experienced diarrhea, but only one patient discontinued treatment after reporting diarrhea with abdominal pain, lethargy, and nausea [24]. Sitbon et al. [20] reported both nausea and dyspepsia in 10 % of patients.

8.2 Ambrisentan

Galié et al. [30] reported that 12.5 % of patients treated with ambrisentan 1, 2.5, 5, and 10 mg once daily developed nausea by week 12, with no significant difference between the treatment groups. In the ARIES-1 trial, abdominal pain and constipation both occurred in 1.5 and 3.7 % more patients, respectively, in the combined treatment groups than in the placebo group. In the ARIES-2 trial, abdominal pain and constipation occurred in 3.1 and 0.9 % more patients, respectively, in the combined treatment groups than in the placebo group. Among the 261 patients receiving ambrisentan in both ARIES trials, one patient withdrew from treatment for gastroenteritis within 12 weeks [31]. At the 2-year follow-up, 1.1 % of the 5 mg once daily group had withdrawn from treatment due to diarrhea and vomiting [32].

The VOLT post-marketing surveillance data has indicated a 7 % incidence of diarrhea and 6 % incidence of nausea in treated patients [34].

9 Fatigue

9.1 Bosentan

In the STRIDE-2 trial, the incidence of fatigue was 5 % in the treatment group and 3.2 % in the placebo group [27]. The Sitbon et al. [20, 24] and BREATHE-5 extension trials reported fatigue in 17 and 5 % of treated patients, respectively.

10 Drug–Drug Interactions

10.1 Cytochrome P450 (CYP) 3A4 Substrates, Inhibitors, and Inducers

As a CYP3A4 substrate, bosentan must be used cautiously in combination with any drug that is a CYP3A4 inducer or inhibitor. Ketoconazole is one CYP3A4 inhibitor that has been shown to increase the area under the concentration–time curve (AUC) of bosentan by twofold. When used together, close monitoring for bosentan toxicity is advised [59]. Conversely, rifampicin (rifampin), a potent CYP3A4 inducer, may decrease the efficacy of bosentan; it has been shown to decrease the AUC of the drug by 58 % after 7 days [60]. As a CYP3A4 inducer, bosentan can decrease the systemic concentration of any drug that is a CYP3A4 substrate. For example, it has been shown to reduce the plasma concentration of simvastatin by 34 %, which has prompted the recommendation of cholesterol monitoring when the two drugs are used in combination [60].

Because ambrisentan is metabolized via CYP3A4 to a much lesser extent than bosentan, it is not as affected by CYP3A4 inducers or inhibitors. Still, ketoconazole does cause a 35 % increase in the AUC of ambrisentan and close monitoring is recommended when the drugs are used in combination [61]. As it is not known to be a CYP3A4 inducer or inhibitor, ambrisentan may be used safely with other CYP3A4 substrates [61].

Macitentan is also a CYP3A4 substrate. Ketoconazole causes a twofold increase in macitentan exposure, and reduces the exposure of its active metabolite by 26 % [62]. Rifampicin decreases the AUC of macitentan by 79 % but does not affect the active metabolite. As rifampicin is expected to significantly decrease macitentan's efficacy, the combination should be avoided [62]. As it is not known to be a CYP3A4 inducer or inhibitor, macitentan may be used safely with other CYP3A4 substrates [62].

10.2 CYP2C9 Substrates

Warfarin is a CYP2C9 substrate that is often prescribed to patients with PAH. As a CYP2C9 inducer, bosentan can decrease warfarin exposure. At four times its therapeutic dose, bosentan causes a 30 % decrease in plasma concentrations of warfarin; however, at therapeutic doses in patients with PAH, warfarin has no significant effect on the international normalized ratio (INR) and no dose adjustment is required [59]. Ambrisentan and macitentan are not CYP2C9 inducers or inhibitors. Neither have a significant effect on warfarin pharmacokinetics or on INR [62, 63].

10.3 Phosphodiesterase-5 Inhibitors

Phosphodiesterase (PDE)-5 inhibitors are often used in combination with ERAs for the management of severe PAH. Concomitant administration of bosentan and sildenafil has been shown to result in a 63 % decrease in the AUC of sildenafil and a 50 % increase in the AUC of bosentan [64]. Ambrisentan and tadalafil, when taken together, do not significantly impact each other's pharmacokinetics [65]. When macitentan and sildenafil are taken in combination, there is a 15 % decrease in the AUC of macitentan and a 15 % increase in the AUC of sildenafil [66]. Based on these studies, no dose adjustment for bosentan, ambrisentan, or macitentan is recommended for patients who also require PDE-5 inhibitors [59, 62, 63].

10.4 Cyclosporine

Cyclosporine (cyclosporine) is a potent immunosuppressive agent that may be used in patients with CTD-associated PAH. As a substrate and moderate inhibitor of CYP3A4, it has the most significant interactions with bosentan. When bosentan and cyclosporine were coadministered, the blood concentrations of cyclosporine decreased by 50 % as a result of bosentan's induction of CYP3A4. More impressively, the bosentan plasma concentrations increased by three- to four-fold at steady state. This effect may even be underestimated, as it does not take into account potential enzyme auto-induction by bosentan. As a result of these findings, the coadministration of these drugs is contraindicated [60]. Similarly, concomitant use of cyclosporine and ambrisentan increases the AUC of ambrisentan by 121 % at steady state but does not affect cyclosporine's pharmacokinetics. As such, when used concomitantly with cyclosporine, the dose of ambrisentan should be limited to 5 mg daily [63]. Interestingly, macitentan and cyclosporine may be used together safely as no interaction between the two drugs has been reported [62].

10.5 Hormonal Contraception

Bosentan, ambrisentan, and macitentan have all been shown to be teratogenic in animal models, and they may

only be prescribed to women of child-bearing age who are using reliable forms of contraception [43, 52, 57]. Bosentan has been shown to decrease the AUC of norethisterone and ethinyl estradiol, two oral contraceptives, by 56 and 66 %, respectively, in individual subjects, likely via CYP3A4 induction. As such, hormonal contraception in any form is not considered reliable when administered with bosentan [60]. Ambrisentan decreases the AUC of norethindrone by 14 % and ethinyl estradiol by 4 %, which is not considered clinically significant. No dose adjustment is required when using ambrisentan with hormonal contraception [61]. The effect of macitentan on the pharmacokinetics of hormonal contraception has not been studied to date. It is, however, not expected to be significant since macitentan is not a CYP3A4 inducer [62].

11 Conclusion

The advent of ERAs marked a significant advancement in the treatment of PAH. With three ERAs approved for treatment of WHO functional class II, III, and IV PAH, the prescribing physician and patient must be aware of the adverse effect profile, tolerability, and potential drug–drug interactions of each agent currently available. While all three agents are generally well-tolerated, mild cardiac, respiratory, neurologic, and gastrointestinal adverse effects may develop on treatment. All three agents are associated with the development of anemia that is usually mild. While bosentan increases a patient's risk of developing liver transaminitis, these effects are often self-limited and may not require discontinuation or dose reduction. Ambrisentan and macitentan do not appear to confer the same risk profile for the liver at this time. A careful review of a patient's medication history is essential prior to initiating ERA therapy. Drug–drug interactions occur with all three ERAs and pose a significant risk to the patient if unchecked.

Acknowledgments No sources of funding were used to assist in the preparation of this review. Meghan Aversa and Sandra Porter have no conflicts of interest that are directly relevant to the content of this review. John Granton is an investigator in trials in pulmonary hypertension sponsored by Actelion Pharmaceuticals Ltd, Eli Lilly and Co., and GlaxoSmithKline Inc., a member of a data safety monitoring committee for Actelion Pharmaceuticals Ltd, and receives consultant fees from Actelion Pharmaceuticals Ltd, Eli Lilly and Co., and GlaxoSmithKline Inc. that are payable to the University Health Network Foundation. Actelion Pharmaceuticals Ltd has supported the University Health Network Foundation to help provide education and research in pulmonary hypertension.

Meghan Aversa, Sandra Porter, and John Granton were responsible for writing and reviewing all drafts of the manuscript and approving the final draft.

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