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Original Article

Clinical efficacy and safety of switch from bosentan to macitentan in children and young adults with pulmonary arterial hypertension

Ebru Aypar, Dursun Alehan, Tevfik Karagöz, Hayrettin Hakan Aykan, İlker Ertugrul

Department of Pediatric Cardiology, Hacettepe University, Sihhiye, Ankara, Turkey

Abstract *Background:* Macitentan is an orally active, potent, dual endothelin receptor antagonist and is the only registered treatment for pulmonary arterial hypertension that significantly reduced morbidity and mortality in a long-term event-driven study. *Aim:* Few studies compared the clinical efficacy and safety of switch from bosentan to macitentan only in adult patients with pulmonary arterial hypertension. We aimed to evaluate the clinical efficacy and safety of switch from bosentan to macitentan in children and young adults. *Methods:* This is a single-institution, 24-week prospective study. Patients ⩾ 12 years of age with idiopathic/heritable pulmonary arterial hypertension or related to CHD or residual pulmonary arterial hypertension due to repaired congenital systemic-to-pulmonary shunts and on bosentan therapy were included. Concomitant treatment with oral phosphodiesterase type 5 inhibitors and inhaled prostanoids was allowed. Outcome measures included change from baseline to week 24, in the 6-minute walk distance, functional class, oxygen saturation at rest/after 6-minute walk distance test, systolic pulmonary artery pressure estimated by echocardiography, and brain natriuretic peptide levels. Safety end points included adverse events laboratory abnormalities. *Results:* A total of 13 patients – 5 male and 8 female – completed the study. The mean age was 20.3 ± 6.5 years (12–35) and weight was 54.0 ± 14.5 kg (27–75). Five patients were ⩽ 18 years of age. Macitentan improved 6-minute walk distance from baseline (mean: 466 ± 35 m (300–590)), at 12 weeks (mean: 494 ± 78 m (325–590), +28 m) ($p < 0.05$), and at 24 weeks (mean: 507 ± 58 m (325–625), +41 m) ($p < 0.05$). Macitentan did not significantly change functional class, oxygen saturation at rest/after 6-minute walk distance test, brain natriuretic levels, and systolic pulmonary artery pressure ($p > 0.05$). None of the patients had anaemia, hepatotoxicity, and peripheral oedema. *Conclusions:* Our study is the first study that showed that switch from bosentan to macitentan significantly improved exercise capacity in children and young adults with pulmonary arterial hypertension and is well tolerated without any adverse events.

Keywords: Bosentan; children; endothelin receptor antagonist; macitentan; pulmonary arterial hypertension

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Pulmonary arterial hypertension is a severe disease characterised by a sustained elevation of pulmonary vascular resistance, ultimately leading to right heart failure and death.[1] Disease progression occurs despite the availability of drugs that are specific for the disorder.[2] Endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, and prostacyclin and its analogues have been approved for the treatment of pulmonary arterial hypertension.[3–9]

Macitentan is an orally active, potent, dual endothelin receptor antagonist developed by modifying the structure of bosentan to increase efficacy and safety and characterised by sustained receptor binding and enhanced tissue penetration.[10–13] Compared with the dual endothelin-A/endothelin-B receptor antagonist bosentan and the endothelin-A selective

Correspondence to: Department of Pediatric Cardiology, Hacettepe University, Ankara, Såhhåye, Turkey. Tel: +90 (312) 305 11 57; Fax: +90 (312) 324 49 90; E-mail: ebruaypar@gmail.com

receptor antagonist ambrisentan, macitentan had slower receptor dissociation kinetics.[12] The safety profile of macitentan appears to be superior with respect to hepatic safety and oedema than bosentan and ambrisentan, respectively.[9,14]

Macitentan's effectiveness was established in the double-blind, randomised, placebo-controlled SERAPHIN study (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve Clinical Outcome) in 2013.[9] The large Phase III study SERAPHIN tested macitentan in more than 700 patients and provided unique long-term outcome data not available for other members of this class.[9,14] Macitentan is the only registered treatment for pulmonary arterial hypertension that significantly reduced morbidity and mortality as a combined end point in SERAPHIN study and is approved in the United States of America, the EU, and various other countries for the treatment of pulmonary arterial hypertension.[9,15,16]

Two studies have compared the clinical efficacy and tolerability of switch from bosentan to macitentan only in adult patients with pulmonary arterial hypertension.[17,18] We aimed to evaluate the clinical efficacy and safety of switch from bosentan to macitentan in children and young adults with pulmonary arterial hypertension because of the desirable features of macitentan, such as once-a-day profile and freedom from monthly liver function tests.

Methods

Study design

The study was designed as a single-institution, 24-week prospective observational study in an existing cohort of pulmonary arterial hypertension patients and was conducted in Hacettepe University Hospital, Department of Pediatric Cardiology, Ankara, Turkey. The institutional ethics committee approved the protocol. Written informed consent was obtained from all patients and/or patients' relatives.

Selection of patients

Patients $\geqslant 12$ years of age who had idiopathic or heritable pulmonary arterial hypertension or related to CHD or residual pulmonary arterial hypertension due to repaired congenital systemic-to-pulmonary shunts and on bosentan therapy were included. Confirmation of pulmonary arterial hypertension with right heart catheterisation was required. Patients were required to have a 6-minute walk distance of 300 m or more to be in class II or III according to the World Health Organization functional classification – an adaptation of the NYHA functional classification. Concomitant treatment with oral phosphodiesterase type 5 inhibitors, inhaled prostanoids, digoxin, oral diuretics, and angiotensin-converting enzyme inhibitors was allowed, provided that the patient had been receiving a stable dose for at least 3 months before the study. Patients with Down syndrome and other syndromes were included. Patients in class IV, receiving intravenous prostanoids, with liver or renal impairment, or any other systemic disease were excluded. Macitentan was approved only in patients $\geqslant 12$ years of age. Therefore, our study group consisted of patients $\geqslant 12$ years of age.

Procedures

Within 1 month after screening, the treatment of patients who were eligible for the study was switched from bosentan to macitentan at a once-daily dose of 10 mg after a 24-hour wash-out period following cessation of bosentan. The maximum plasma concentrations of macitentan are reached in ~ 8 hours, and macitentan had elimination half-life of ~ 16 hours. We provided a wash-out period to avoid hepatotoxicity and hypotension, when taking bosentan and macitentan consecutively, by taking a risk that patients on monotherapy did not take any specific treatment for a definite time interval.[13,17,18] Patients on combination treatment continued oral phosphodiesterase type 5 inhibitors and inhaled prostanoids. Clinical assessment – including physical examination, 6-minute walk distance test, and functional class – and transthoracic echocardiography were performed by the same cardiologist. Laboratory data, such as haemoglobin, alanine aminotransferase, aspartate aminotransferase, and brain natriuretic peptide levels, were obtained at screening, beginning of the study, and at 12th and 24th weeks. Adverse events such as anaemia, hepatotoxicity, peripheral oedema, or others were recorded throughout the treatment period.

Outcome measures

Outcome measures included change from baseline to week 24, in the 6-minute walk distance, functional class, oxygen saturation at rest and after 6-minute walk distance test, systolic pulmonary artery pressure estimated by echocardiography, and brain natriuretic peptide levels. Safety end points included adverse events and laboratory abnormalities.

Statistical analysis

Change in 6-minute walk distance from baseline to week 12 and week 24 was analysed by repeated measures (within subjects) analysis of variance. Oxygen saturations, at rest and after 6-minute walk distance test, systolic pulmonary arterial pressures

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estimated by echocardiography, and brain natriuretic peptide levels at 12 and 24 weeks were compared with those at baseline using Friedman's test. Non-parametric correlations – that is association between disease duration, bosentan duration, number of specific drugs, and 6-minute walk distance at 12th and 24th weeks – were evaluated by Spearman's rank-order correlation (ρ) coefficient. A p value of less than 0.05 was considered to indicate statistically significant difference. The data analysis was performed by using IBM SPSS Statistics 23 software.

Results

A total of 13 patients – 5 male and 8 female – completed the study. The mean age was 20.3 ± 6.5 years (12–35) and body weight was 54.0 ± 14.5 kg (27–75). Five patients were ⩽ 18 years of age. Six patients had pulmonary arterial hypertension related to CHD and Eisenmenger syndrome, four patients had residual pulmonary arterial hypertension due to repaired congenital systemic-to-pulmonary shunts, and three patients had idiopathic pulmonary arterial hypertension. A total of 11 patients were in World Health Organization functional class II, and 2 patients were in World Health Organization functional class III. Mean duration of pulmonary arterial hypertension was 10.2 ± 6.7 years (2–22) and patients were on bosentan for 5.8 ± 3.1 years (1–13). Six patients were on monotherapy (bosentan) and seven patients were on combination therapy. Two patients with Down syndrome could not perform 6-minute walk distance test. One patient had Turner syndrome and was able to perform the test. Clinical characteristics of the study patients and 6-minute walk distance test results are shown in Table 1.

Macitentan improved exercise capacity (6-minute walk distance) from baseline (mean: 466 ± 35 m (300–590)), at 12 weeks (mean: 494 ± 78 m (325–590), +28 m) ($p < 0.05$), and at 24 weeks (mean: 507 ± 58 m (325–625), +41 m) ($p < 0.05$) (Figs 1 and 2). We did not observe any statistically significant difference in 6-minute walk distance between 12th and 24th weeks ($p < 0.05$). Functional class of the patients remained unchanged in all patients. Macitentan did not significantly change resting oxygen saturation levels from baseline (median: 88% (60–99)), at 12 weeks (median: 91% (69–99)), and at 24 weeks (median: 93% (60–98)); oxygen saturation levels after 6-minute walk distance test from baseline (median: 87% (55–99)), at 12 weeks (median: 92% (55–99)), and at 24 weeks (median: 89% (60–97)); brain natriuretic peptide levels from baseline (median: 30 pg/ml (10–384)), at 12 weeks (median: 20 pg/ml (10–326)), and at 24 weeks (median: 62 pg/ml (10–362)) (upper limit of normal < 100 pg/ml); and systolic pulmonary arterial pressure estimated by echocardiography ($p > 0.05$).

We did not find any significant correlation, in the 6-minute walk distance, between disease duration and change from baseline to week 24 ($p > 0.05$), between bosentan duration and change from baseline to week 24 ($p > 0.05$), and between number of specific drugs and change from baseline to week 24 ($p > 0.05$).

We did not find any statistically significant difference between children and adults with respect to change from baseline to week 24, in the 6-minute walk distance ($p > 0.05$).

None of the patients had anaemia, hepatotoxicity, peripheral oedema, or any other adverse events.

Discussion

According to our preliminary results, in children and young adults with pulmonary arterial hypertension, switch from bosentan to macitentan significantly improved exercise capacity – 6-minute walk distance test – at 24 weeks (+41 m) compared with baseline ($p < 0.05$).

Few studies have been published in literature that compared the clinical efficacy and tolerability of switch from bosentan to macitentan only in adult patients with pulmonary arterial hypertension.[17,18] Blok et al evaluated the effect of a switch from bosentan to macitentan on clinical status after 24 weeks in 40 adult patients with pulmonary arterial hypertension due to CHD (mean age: 45 ± 13 years, 40% male, 40% Down, 75% Eisenmenger)[17]. End points were change in functional class, NT-pro-brain natriuretic peptide levels, tricuspid annular plane systolic excursion, 6-minute walk distance, resting oxygen saturation, ferritin levels, and adverse events. The median treatment duration on bosentan was 7.2 years. Ten (25%) patients were on bosentan–sildenafil combination therapy, 52% of patients were in World Health Organization functional class II, and 48% were in class III.

We evaluated the effect of switch in a younger patient population (13 patients, mean age: 20.3 ± 6.5 years (12–35)). Our study included the youngest patients compared with other studies, and five of our patients were children. We included not only patients with pulmonary arterial hypertension related to CHD as in Blok et al's study, but also patients with idiopathic/heritable pulmonary arterial hypertension. We were unable to make statistical comparison in 6-minute walk distance according to different pulmonary arterial hypertension aetiology owing to a small number of patients.

Our median treatment duration of bosentan was 5.8 ± 3.1 years (1–13), similar to Blok et al's

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Table 1. Clinical characteristics of the study patients and 6-minute walk distance test results.

Patient no.	Age (years)	Weight (kg)	Sex	Diagnosis	PAH duration (years)	WHO FC	Bosentan duration (years)	PAH treatment	6-MWD baseline (m)	6-MWD 12 weeks (m)	6-MWD 24 weeks (m)
1	12	27	M	Operated VSD, CC-TGA, residual PAH	6	II	6	Bosentan	490	560	585
2	25	57	M	Large PDA, Eisenmenger syndrome	13	II	13	Bosentan	455	500	510
3	17	78	F	Idiopathic PAH	4	II	4	Bosentan, PDE-5 inhibitor	580	590	625
4	12	48	M	Idiopathic PAH	3	II	3	Bosentan, PDE-5 inhibitor, inhaled prostanoids	590	540	580
5	20	51	F	Operated multiple VSD, residual PAH	12	II	7	Bosentan	405	490	435
6	23	73	F	Down syndrome, complete AVSD, Eisenmenger	22	II	7	Bosentan	Down	Down	Down
7	26	68	F	Large PDA, Eisenmenger	7	II	7	Bosentan	545	575	590
8	18	55	F	Large VSD, Eisenmenger	17	II	6	Bosentan, PDE-5 inhibitor, inhaled prostanoids	450	425	475
9	13	45	F	Turner syndrome, transcatheter embolisation of PDA, residual PAH	7	III	7	Bosentan, PDE-5 inhibitor, inhaled prostanoids	300	325	325
10	20	50	F	Down syndrome, complete AVSD, Eisenmenger	19	III	6	Bosentan, PDE-5 inhibitor, inhaled prostanoids	Down	Down	Down
11	35	64	M	Operated VSD, residual PAH	2	II	1	Bosentan	405	450	450
12	19	58	M	Idiopathic PAH	5	II	1	Bosentan, PDE-5 inhibitor, inhaled prostanoids	475	525	550
13	24	32	F	DORV, VSD, Eisenmenger	16	II	7	Bosentan, inhaled prostanoids	430	450	450
Mean ± SD (range)	20.3 ± 6.5 years (12–35)	54.0 ± 14.5 kg (27–75)			10.2 ± 6.7 years (2–22)		5.8 ± 3.1 years (1–13)		466 ± 35 m (300–590)	494 ± 78 m (325–590)	507 ± 58 m (325–625)

6-MWD = 6-minute walk distance; ACE = angiotension-converting enzyme; AVSD = atrioventricular septal defect; CC-TGA = congenitally corrected transposition of great arteries; DORV = double-outlet right ventricle; PAH = pulmonary arterial hypertension; PDA = patent ductus arteriosus; PDE-5 = phosphodiesterase type 5 enzyme; VSD = ventricular septal defect; WHO FC = World Health Organization functional class

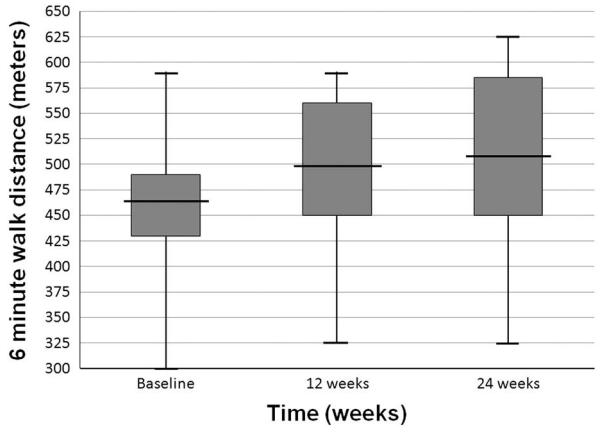

Figure 1.
Effect of switch from bosentan to macitentan on 6-minute walk distance over time in patients with pulmonary arterial hypertension.

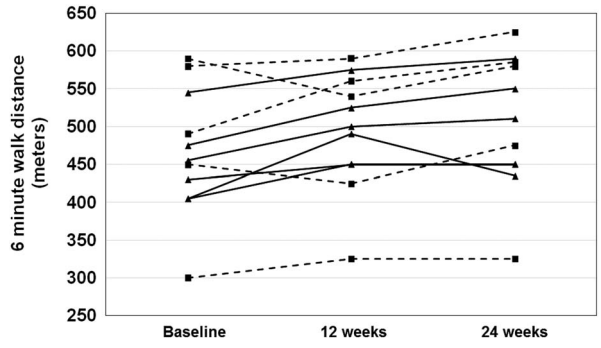

Figure 2.
Comparison of children (⩽18 years) and adult patients (>18 years) with respect to change from baseline to week 24, in the 6-minute walk distance. No statistically significant difference was found between children and adults ($p > 0.05$). Dotted lines show children.

study. Although Blok et al reported improvement in functional class (number of patients in functional class III or IV decreased from 48 to 23%), tricuspid annular plane systolic excursion, and NT-pro-brain natriuretic peptide levels, they did not observe any change in 6-minute walk distance, resting oxygen saturations, and ferritin levels. They proposed that the relatively high number of Down syndrome patients (40%) in their cohort might have influenced the overall 6-minute walk distance test results. We observed improvement in 6-minute walk distance. Only two of our patients had Down syndrome and could not perform 6-minute walk distance test. This relatively small number of patients with Down syndrome (15%) compared with Blok et al's cohort (40%) might explain our results.

In our study, functional class of the patients and brain natriuretic peptide levels remained unchanged. A total of 11 patients were in functional class II and 2 patients were in functional class III; the small number of patients in functional class III might have affected our results. Blok et al also did not report any change in functional class II patients. In addition, in the SERAPHIN study with macitentan, functional class improved from baseline to month 6 in 13% of the patients in the placebo group, as compared with 22% of those in the group that received 10 mg of macitentan.[9]

In Blok et al's study, the number of patients with hospitalisation and syncope did not change, and no serious adverse events were recorded. Liver function tests remained and >1 mmol/L drop in haemoglobin was seen in two patients. One patient died because of sepsis. In our study, none of our patients died or had clinical worsening. The authors concluded that adult patients with pulmonary arterial hypertension due to CHD currently using bosentan might improve from a switch to macitentan under careful follow-up.

In Blok et al's study, resting oxygen saturation levels did not change significantly and oxygen saturation levels after 6-minute walk distance test were not evaluated.[17] We also did not observe any statistically significant change in both ($p > 0.05$).

Safdar et al evaluated the tolerability of switch to macitentan from bosentan in 24 adult patients with pulmonary arterial hypertension.[18] The mean age was 58 ± 13 years, duration of the disease was 6.6 ± 4.4 years, and follow-up duration was 5.7 ± 1.5 months. Switch from bosentan to macitentan was well tolerated and safe with no significant change in oedema and liver enzyme levels. Functional class was maintained. Three months following the switch, no significant change was seen in the 6-minute walk distance and brain natriuretic peptide levels. Two patients did not tolerate the switch and had to be returned to bosentan. One patient with portopulmonary hypertension developed elevated alanine aminotransferase and aspartate aminotransferase, and the second patient's macitentan was stopped because of malaise and tachyarrhythmia.[18] We observed an improvement in 6-minute walk distance test (+28 m) even 3 months after the switch. In Safdar et al's study, 30% of the patients had pulmonary arterial hypertension related to connective tissue disease, 25% had idiopathic pulmonary arterial hypertension, and 21% had pulmonary hypertension related to CHD. We propose that macitentan might have a different effect on pulmonary arterial hypertension patients with respect to aetiology, and the effect of switch from bosentan to macitentan in various pulmonary arterial hypertension patients requires further investigation.

Although the most common laboratory abnormality with macitentan was reported as anaemia in the SERAPHIN trial (a haemoglobin level of <8 g/dl occurred in 4.3% of the macitentan group and 0.4% of the placebo group), we did not observe any drop in haemoglobin levels.[9] In the SERAPHIN trial, the

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incidence of peripheral oedema and hepatotoxicity was similar across macitentan and placebo groups. In addition, the incidence of headache and nasopharyngitis was higher with macitentan than with placebo.[9] In our study, switch from bosentan to macitentan was well tolerated without these adverse events.

Study limitations

The present study was a short-term study with a small number of patients. Our patients had pooling of diagnoses, only included patients with idiopathic/heritable pulmonary arterial hypertension, related to CHD, or residual pulmonary arterial hypertension. Effect of switch from bosentan to macitentan in various pulmonary arterial hypertension patients was not evaluated.

We performed only routine measurements – such as change in 6-minute walk distance, functional class, oxygen saturation at rest and after 6-minute walk distance test, systolic pulmonary arterial pressure estimated by echocardiography, and serum brain natriuretic peptide levels. Haemodynamic data by cardiac catheterisation, before and after the switch, were not available and would have provided more valuable data.

This was a single-arm study in which we did not compare the results with a placebo group. Our study was an unblinded study showing an end point that has a degree of patient effort (change in 6-minute walk distance), which could bias the study.

Conclusions

Our study is the first study that showed that switch from bosentan to macitentan significantly improved exercise capacity in children and young adults with pulmonary arterial hypertension and is well tolerated without any adverse events.

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Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the ethics committee of Hacettepe University. Informed consent was obtained from all individual patients and/or parents.

References

1. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015; 46: 903–975.
2. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from REVEAL. Chest 2012; 142: 448–456.
3. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. Lancet 2001; 358: 1119–1123.
4. Olschewski H, Simonneau G, Galiè N, et al. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002; 347: 322–329.
5. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 2002; 346: 896–903.
6. Galiè N, Badesch BD, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 2005; 46: 529–535.
7. Galiè N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 2005; 353: 2148–2157; (Erratum, N Engl J Med 2006;354:2400–2401).
8. Galiè N, Brundage B, Ghofrani A, et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009; 119: 2894–2903; (Erratum, Circulation 2011;124:e279).
9. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013; 369: 809–818.
10. Bolli MH, Boss C, Binkert C, et al. The discovery of N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N′-propylsulfamide (macitentan), an orally active, potent dual endothelin receptor antagonist. J Med Chem 2012; 55: 7849–7861.
11. Iglarz M, Binkert C, Morrison K, et al. Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. J Pharmacol Exp Ther 2008; 327: 736–745.
12. Gatfield J, Mueller Grandjean C, Sasse T, et al. Slow receptor dissociation kinetics differentiate macitentan from other endothelin receptor antagonists in pulmonary arterial smooth muscle cells. PLoS One 2012; 7: e47662.
13. Keating GM. Macitentan: a review in pulmonary arterial hypertension. Am J Cardiovasc Drugs 2016; 16: 453–460.
14. Dingemanse J, Sidharta PN, Maddrey WC, et al. Efficacy, safety and clinical pharmacology of macitentan in comparison to other endothelin receptor antagonists in the treatment of pulmonary arterial hypertension. Expert Opin Drug Saf 2014; 13: 391–495.
15. Actelion Pharmaceuticals US Inc. Opsumit® (macitentan) tablets, for oral use: US prescribing information. 2016. http://opsumit.com/.
16. European Medicines Agency. Opsumit (macitentan): EU summary of product characteristics. 2016. http://www.ema.europa.eu/.
17. Blok IM, van Riel AC, van Dijk AP, Mulder BJ, Bouma BJ. From bosentan to macitentan for pulmonary arterial hypertension and adult congenital heart disease: further improvement? Int J Cardiol 2017; 227: 51–52.
18. Safdar Z, Thakur A, Frost A. Tolerability of switch to macitentan from bosentan in pulmonary arterial hypertension. South Med J 2017; 110: 223–228.