

Macitentan for the treatment of pulmonary arterial hypertension: a review of the literature for the recently approved endothelin receptor antagonist

Abstract

Purpose: The pharmacokinetic profile, clinical efficacy, and safety of this recently approved dual endothelin receptor antagonist for the treatment of pulmonary arterial hypertension (PAH) are reviewed.

Summary: Macitentan was recently approved by the Food and Drug Administration as an alternative oral option for patients with PAH and is available as a 10 mg tablet to be administered once daily. The pivotal Phase III clinical trial, SERAPHIN, was a large double-blind, multi-center, placebo-controlled study (n=742) designed to evaluate the long-term safety and efficacy of macitentan in patients with symptomatic PAH. The study was associated with a reduced risk of morbidity and mortality events versus placebo by 45% in the 10mg group. The incidence of adverse events found in SERAPHIN was mostly similar across all groups. Liver enzyme tests and hemoglobin should be obtained prior to initiation and may be repeated during treatment as clinically indicated. Drug interactions with macitentan appear to be less significant than with bosentan, and there are no known drug contraindications. Macitentan is a pregnancy category X drug, so a Risk Evaluation and Mitigation Strategy (REMS) program is required for all females to obtain macitentan.

Conclusions: Macitentan is an effective oral therapy for PAH in addition to standard treatment regimens.

Keywords: macitentan, pulmonary arterial hypertension, endothelin receptor antagonist

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Abbreviations: PAH, pulmonary arterial hypertension; FDA, food and drug administration; ET, endothelin; C_{max} , maximum plasma drug concentration; REMS, risk evaluation and mitigation strategy; SERAPHIN, study with an endothelin receptor antagonist in pulmonary arterial hypertension to improve clinical outcome; WHO, world health organization; AWP, average wholesale price

Introduction

Pulmonary arterial hypertension (PAH) is a progressive and chronic disease affecting about 15 to 50 people per million, women more than men.^{1,2} PAH is a cardiopulmonary condition that is characterized by sustained elevation of mean pulmonary arterial pressure (mPAP) of ≥ 25 mmHg at rest in the absence of other causes of pulmonary hypertension which ultimately progresses to right heart failure.³ Symptoms typically include fatigue, dyspnea, chest pain, dizziness, and ankle/pedal edema.³ Symptom severity is graded by the World Health Organization (WHO) functional classes with I being the least severe and IV being the most severe. This complex and debilitating disease is associated with significant morbidity and mortality.³

Although treatment of the underlying etiology is the ideal approach for managing pulmonary hypertension, options for PAH are limited. Therefore, therapy to treat the pulmonary hypertension itself is required. This includes endothelin receptor antagonists (bosentan and ambrisentan), phosphodiesterase type 5 inhibitors (sildenafil and tadalafil), calcium-channel blockers (diltiazem, nifedipine, and amlodipine), and prostanoids (epoprostenol, treprostinil, and

iloprost).³ Additional PAH treatment options recently available include riociguat, a soluble guanylate cyclase stimulator and treprostinil in an oral extended release dosage form. Treatment regimens vary based on severity of disease, patient preference, compliance, and medication characteristics.

The pathogenesis of PAH involves remodeling of the pulmonary arterioles, including vasoconstriction and smooth muscle and endothelial cell proliferation. These changes lead to progressive increases in pulmonary vascular resistance and subsequent right heart failure. One of the major pathways in PAH involves dysregulation of endothelin (ET), a peptide produced by endothelial cells that acts on both the ET-A and ET-B receptors in the lung. In October 2013, the Food and Drug Administration (FDA) approved a new agent, macitentan, in the class of endothelin receptor antagonists, for the treatment of adults with PAH. This article focuses on the pharmacology, clinical efficacy, pharmacokinetics, pharmacodynamics, safety, and drug interactions of macitentan.

Discussion

Chemistry and Pharmacology

Macitentan (Opsumit, Actelion Pharmaceuticals US, Inc.) is a new dual ET_A/ET_B endothelin (ET) receptor antagonist for the treatment of PAH. Endothelin (ET)-1 and its receptors (ET_A and ET_B) cause a variety of harmful effects, such as potent vasoconstriction, fibrosis, cell proliferation, and inflammation. The pathogenesis of

PAH is characterized by upregulation of the local ET system which contributes to adverse hemodynamic effects, vascular remodeling, and disease progression.⁴

Blockade of this pathway with ET receptor antagonists including bosentan and ambrisentan improves 6-minute walk distance and is associated with a longer time to clinical worsening compared to placebo.^{5,6} Macitentan was developed to have a high potency against both ET_A and ET_B, substantial tissue penetration, and a long duration of action facilitating once-daily dosing.⁷

Pharmacokinetics and pharmacodynamics: The pharmacokinetics of macitentan have been primarily evaluated in healthy volunteers with and without renal or hepatic impairment. In patients with PAH, drug exposure is similar to that in healthy individuals, and there are no clinically relevant effects of age, sex, or race. At doses between 1 and 30mg, the pharmacokinetics of macitentan are dose proportional.⁸ In plasma, macitentan has an active metabolite, ACT-132577, which has affinity for ET_A and ET_B but is about 20% as potent as the parent compound⁹ (Figure-1).⁷

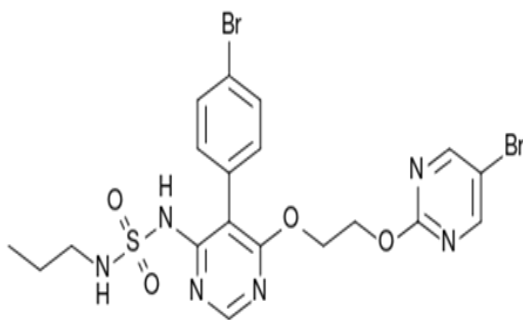


Figure 1 Macitentan chemical structure.

Absorption: After oral administration, macitentan is slowly absorbed due to its low aqueous solubility, and the median time to reach maximum plasma drug concentration (C_{max}) is approximately eight hours¹⁰ Fat intake does not influence the absorption of macitentan so it may be taken with or without food. The absolute bioavailability is unknown.⁸

Distribution: Both macitentan and its active metabolite (ACT-132577) are highly protein bound (>99%), primarily to albumin but also to alpha-1-acid glycoprotein.⁸ Both have large volumes of distribution ($V_d=50$ liters for macitentan and $V_d=40$ liters for its active metabolite).⁸

Metabolism: The active metabolite of macitentan (ACT-132577) also exhibits ET_A and ET_B receptor antagonism and is formed by oxidative depropylation. This is catalyzed primarily by the cytochrome P450 isoenzyme CYP3A4, with a minor contribution from CYP2C19. An inactive carboxylic acid metabolite, ACT-373898, is also present in plasma.^{8,11}

One study evaluated the potential for macitentan to inhibit or induce CYP3A4, as bosentan is a mild-to-moderate enzyme inducer. Changes in urinary 6-beta-hydroxycortisol/cortisol ratio suggested CYP3A4 enzyme induction with increasing doses of macitentan while no effect was found with placebo.¹² An increased ratio indicates induction and decreased ratio indicates inhibition. At a dose of 10 mg, macitentan increased this ratio 39.1%, compared with 60% for bosentan and 137% for rifampicin.^{13,14}

Macitentan was studied in patients with severe renal impairment (creatinine clearance 15-29mL/min) and in patients with varying degrees of hepatic impairment (Child-Pugh Class A, B, and C). There was less exposure to macitentan and its active metabolite in hepatically impaired patients although this did not correlate with the degree of hepatic impairment. Exposure was slightly increased in patients with severe renal insufficiency. These differences are not considered clinically relevant, and no dose adjustments are recommended for either renal or hepatic impairment.¹⁵

Elimination

Fifty percent of macitentan is excreted in urine as several inactive metabolites compared with ~25% in feces as a combination of parent drug and metabolites, including the active metabolite ACT-132577.¹¹ The elimination half-life of macitentan and its active metabolite are 17.5hours and 48hours, respectively. With repeated dosing, accumulation of the metabolite is expected to contribute to the medication's clinical effects.¹²

Efficacy

FDA approval of macitentan was based on a pivotal Phase III trial. At the time of writing this article, there are no human clinical studies comparing macitentan with other ERAs, nor are there studies comparing macitentan with other drugs indicated for PAH. SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) is a large double-blind, multi-center, placebo-controlled study designed to evaluate the long-term safety and efficacy of macitentan in patients with symptomatic PAH. A total of 742 patients were randomized to receive placebo (n=250), macitentan 3mg (n=250), or macitentan 10 mg (n=242). Participants were required to be 12years or older and have PAH confirmed with right heart catheterization and classified as World Health Organization (WHO) class II, III, or IV. Stable background oral or inhaled PAH therapy (other than an ERA) was allowed. This could include concomitant oral phosphodiesterase type 5 inhibitors, oral or inhaled prostanoids, calcium-channel blockers, or L-arginine. Patients receiving intravenous or subcutaneous prostanoids were excluded.

The primary end point evaluated was time from treatment initiation to the first morbidity or mortality event in all randomized patients. This composite endpoint of death, atrial septostomy, lung transplantation, initiation of intravenous or subcutaneous prostanoids, or worsening of PAH, was blindly and independently adjudicated. Worsening of PAH was defined by occurrence of all three of the following events: 1) at least 15% decrease from baseline in 6-minute walk distance, confirmed by a second 6-minute walk test on a different day within 2weeks; 2) worsening PAH symptoms; and 3) need for additional PAH treatment. Worsening of PAH symptoms was defined as at least one of the following: a change from baseline to a higher WHO functional class (or no change in patients who were in WHO functional class IV); or appearance or worsening signs of right heart failure that were unresponsive to oral diuretics.¹⁶

Macitentan reduced the risk of occurrence of morbidity and mortality events (46.4% [116/250] for placebo, 38% [95/250] for macitentan 3 mg, and 31.4% [76/242] for macitentan 10 mg). The hazard ratio for the 3 mg group versus placebo was 0.7 (97.5% CI, 0.52 to 0.96; P=0.01) and the hazard ratio for the 10 mg group versus placebo was 0.55 (97.5% CI, 0.39 to 0.76; P<0.001). The

most frequent primary end-point event was worsening of pulmonary arterial hypertension which was reduced from 37.2% in the placebo group to 24.4% in the macitentan 10mg group.

Secondary endpoints included the composite of mortality due to PAH or hospitalization for PAH. This secondary endpoint was also significantly reduced with macitentan 10mg daily compared with placebo (20.7% vs. 33.6%; HR, 0.5; 97.5% CI, 0.34 to 0.75; $p < 0.001$) and with macitentan 3 mg compared with placebo (26% vs. 33.6%; HR, 0.67; 95% CI, 0.46 to 0.97; $p = 0.01$). The most frequent secondary endpoint event was decreased rates of hospitalization in the macitentan groups compared with the placebo group. At month 6, improvement of WHO functional class from baseline was observed in 22%, 20%, and 13% of patients in the macitentan 10mg, macitentan 3mg, and placebo groups, respectively.

While many other PAH trials have been short term and focused on symptoms or surrogate endpoints, SERAPHIN was an event-driven trial which evaluated morbidity and mortality endpoints. Patients were treated for a median duration of 115 weeks and followed for a median of 129 weeks. The significant differences found between placebo and macitentan groups were mainly driven by improvements in worsening of PAH, though mortality rates were low overall.¹⁶ The authors concluded that macitentan significantly decreased morbidity and mortality compared to placebo.

Since FDA approval, macitentan has been added to the American College of Chest Physicians 2014 guideline for pharmacologic therapy for pulmonary hypertension as well as the 2013 World Symposium on Pulmonary Hypertension updated treatment algorithm as an option in PAH patients with WHO functional class II-IV.^{17,18}

Safety profile

Incidence of adverse events found in SERAPHIN were mostly similar across placebo, macitentan 3 mg, and macitentan 10mg groups. One or more serious adverse events occurred in 55%, 52%, and 45% of each group, respectively.¹⁶ The safety profiles across the class of ERAs are similar with a few notable differences. Hepatotoxicity appears to occur less frequently with macitentan compared with bosentan, though the incidence of anemia from macitentan is higher.^{8,16} Other adverse events that were reported include upper respiratory tract infection, bronchitis, nasopharyngitis, and headache.

Hepatotoxicity: While hepatotoxicity is a major concern with bosentan (boxed warning), this adverse effect did not manifest with macitentan in SERAPHIN. Incidence of alanine aminotransferase or aspartate aminotransferase levels elevated more than three times the upper limit of normal were similar across all groups (placebo 4.5%, macitentan 3mg 3.6%, macitentan 10mg 3.4%).¹⁶ Liver enzyme tests should be obtained prior to initiation and may be repeated during treatment as clinically indicated.⁸ Patients should be advised to report symptoms suggesting hepatic injury.⁸

Anemia: Incidence of anemia was higher in the macitentan groups compared with placebo (8.8% and 13.2% for 3mg and 10mg, respectively, compared with 3.2% for placebo). Hemoglobin should be obtained prior to initiation and may be repeated during treatment as clinically indicated.⁸ Initiation of macitentan is not recommended in patients with severe anemia.⁸

Pregnancy and Lactation: Teratogenicity is a class effect of ERAs. Macitentan is a pregnancy category X drug, as are the other agents

in its class. By definition, the risk of the drug in pregnancy clearly outweighs any possible benefit. Macitentan was teratogenic in rabbits and rats at all doses tested.^{8,19}

Due to this reason, a Risk Evaluation and Mitigation Strategy (REMS) program is required for all females to obtain macitentan. Similar to the REMS program for bosentan and ambrisentan, requirements include prescriber certification and enrollment of female patients in a restricted distribution program and participation from registered pharmacies. It is imperative to monitor pregnancy status prior to initiation and on a monthly basis for continuation of therapy.¹⁹

Though it is unknown whether macitentan is present in human milk, it is present in the milk of lactating rats.⁸ Therefore, it is not recommended that nursing mothers concomitantly use macitentan.

Drug interactions

ERAs as a class have distinct drug-drug interaction profiles. Bosentan is prone to drug interactions and concomitant administration with several drugs is either contraindicated or necessitates dose adjustments. Ambrisentan has a more favorable drug interaction profile. Drug interactions with macitentan appear to be less significant than with bosentan but there is still the risk of interactions with several medications.²⁰

Macitentan is primarily metabolized by CYP3A4 and to a lesser extent by CYP2C19. Drug interaction studies demonstrated that strong CYP3A4 inducers and inhibitors have a significant impact on macitentan concentrations.^{8,20-22}

It is recommended to avoid coadministration of macitentan with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) or inducers (e.g. rifampin). The concomitant use of these agents with macitentan can increase or decrease levels, respectively.^{8,20-22}

Data from *in vitro* studies of the drug demonstrated at plasma levels obtained with dosing at 10 mg once daily, macitentan has no relevant inhibitory or inducing effects on CYP enzymes, and is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1).²⁰⁻²²

Though urinary 6-beta-hydroxycortisol/cortisol ratio studies indicate that macitentan may lead to mild induction of CYP3A4, this effect is not considered clinically relevant.

Cost and adherence considerations: Macitentan is similar in cost compared with other agents in its class. The drug is manufactured as a 10mg tablet which should be administered whole, not split, crushed or chewed. Macitentan is available as a 15-count blister pack or 30-count bottle. The recommended dosage is 10 mg by mouth once daily without regards to meals. Since macitentan is a once daily drug, adherence to therapy is optimized.

All 3 drugs are available only as branded products and are accessible only through REMS programs; ambrisentan and macitentan may be acquired by male patients without restriction. Bosentan, approved in 2001, should be available in generic form in November 2015.²² (Table 1).⁷

On evaluation of macitentan for formulary consideration, overall healthcare costs should be considered, as macitentan is similar in cost to other agents within its class.²²

Table 1 Cost comparison of endothelin receptor antagonists

Drug	Dosage form	AWP ^a	Dosage range	Treatment cost/day (based on awp and dosage range)
Macitentan	10mg tablets	\$287.40/ tablet	10mg	\$287.40/day
Bosentan	62.5mg and 125mg tablets	\$164.40/ tablet	125-250mg/day	\$328.80/day
Ambrisentan	5mg and 10mg tablets	\$294.76/ tablet	5-10mg/day	\$294.76/day

AWP, average wholesale price

Conclusion

Prostacyclin analogues remain the most effective agents for managing PAH but their use is hampered by the need for parenteral therapy. Additional therapies are emerging for PAH with several in various stages of development.²³ Macitentan, a dual ET receptor antagonist, is an alternative treatment for patients with symptomatic PAH with long-term morbidity and mortality data demonstrating its efficacy. Macitentan possesses significant tissue distribution, its receptor binding capacity is better than that of bosentan (which allows for a reduced dose), and it has fewer drug-drug interactions than bosentan (which may lead to improved tolerability). Future trials are warranted to determine macitentan's bioavailability, durability, and magnitude of effect in subgroup of patients with PAH and its impact on survival.

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Conflict of interest

The author declares no conflict of interest.

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