Research and Reviews: Journal of Pharmaceutical Quality Assurance

A Comprehensive Drug Review on Macitentan: A Preeminent Inclusion to Pulmonary Arterial Hypertension Therapy

Dherya Bahl[1], Rakesh K. Jaiswal[1], Manzar Ahsan[1], Farha Bano[1], Monika Anand[1], Danish Khan[1], Asif Husain[1]*, Aftab Ahmad[2]*, Fahad A. Al-Abbasi[3], Shah Alam Khan[4]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi-110062, India

[2]Health Information Technology Department, Jeddah Community College, King Abdulaziz University, P.O. Box-80283, Jeddah-21589, Kingdom of Saudi Arabia.

[3]Department of Biochemistry, Faculty of Sciences, King Abdulaziz University, Jeddah 21589, Kingdom of Saudi Arabia

[4]Department of Pharmacy, Oman Medical College, Muscat, Sultanate of Oman

Research Article

Received Date: 02/04/2015
Accepted date: 11/06/2015
Publishing Date: 18/06/2015

***For Correspondence**

Dr. Asif Husain, Sr. Asst. Professor, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Hamdard University, New Delhi-110 062, India.
Tel: +91-11-26059681, 26059688, Ext. 5647;
Mobile- +91-989-1116086;
Fax-+91-11-26059686;
E-mails: drasifhusain@yahoo.com, ahusain@jamiahamdard.ac.in

Dr. Aftab Ahmad, Health Information Technology Department, Jeddah Community College, King Abdulaziz University, P.O. Box-80283, Jeddah-21589, Kingdom of Saudi Arabia.
Tel: +966-02-2870026, Extn.102;
Mobile: +966–507243943;
Fax: +966-02-2870024
E-mails: aftab786sa@hotmail.com, abdulsalam@kau.edu.sa

Keywords: Hypertension, Macitentan, Receptor, Antagonist

ABSTRACT

Macitentan is a radically novice oral orphan drug which was approved by FDA in Oct 2013 (under trade name Opsumit®). It belongs to the class of the endothelin receptor antagonist (ETRA) and is indicated for the treatment of pulmonary arterial hypertension (PAH). PAH is a chronic disorder of raising blood pressure in the artery between the aisle of heart and lung. Till the date, the disease remains incurable and possesses a poor prognosis. A ray of hope in this direction is shown by Macitentan, which has been proved beneficial in decreasing disease progression symptoms and reducing hospitalization. Phase III SERAPHIN trials clearly indicate that it improves morbidity, mortality and 6MWD data compared with other drugs of the same class. Furthermore, its use is seemingly increasing for the treatment of other cardiovascular disorders related to ET system. However, the pharmacokinetics dose adjustments of Macitentan in patients with renal or hepatic impairment are extraneous. Drug–drug interactions are occult, and one circulating pharmacologically active metabolite (ACT-132577) is omnipresent. The safety profile of Macitentan is superior to other drugs of same ETRA's class with prolonged receptor binding properties, greater tissue penetration, hepatic safety, edema/ fluid retention and easy dosing, but it is similar when the decrease in hemoglobin concentration is taken into account. Macitentan attributes, hence, are appended and revolutionary important in the therapeutic long-term treatment and a better alternative remedy for PAH. The present review thus delineates the complete drug profile of Macitentan from the data of studies carried out till date and alleges it as a sanguine future for an overall improved CVS healthcare contributor.

INTRODUCTION

Macitentan, or ACT-064992, proprietary- Opsumit®, is a result of a tailored drug discovery program of Actellion Pharmaceuticals Ltd. [1] in collaboration with Japanese licensee Nippon Shinyaku Co. Ltd [2]. It is a novel orphan medication [3], primarily seen

as a potential candidate for the treatment of pulmonary arterial hypertension (PAH) [4-6] to delay the progression of symptoms; including death, initiation of i.v./s.c. prostanoids [7,8], or clinical worsening of PAH, and worsened PAH symptoms [9]. It also reduces hospitalization for PAH [9,10,11]. It acts via oral route [2], with prolonged receptor binding properties [3] and a greater tissue penetration [12], a tissue targeting [13], non-peptide, dual endothelin receptor antagonist [14] or blocker (ET-A & ET-B), (10) on blood vessels and smooth muscle with both a high affinity and a long residence time [6]. It blocks the stimulation of vasculature hypertrophy, inflammation, fibrosis, proliferation, and vasoconstriction [6], on account of which it is considered as a novel molecule in the treatment of cardiovascular disorders such as heart failure, angina pectoris, pulmonary and systemic hypertension and erectile dysfunction [2,15].

This drug basically blocks endothelin-1, which helps to reduce the blood pressure in the lungs and improves exercise ability [2,9]. Furthermore, some renal, cardiac and retinal changes in type-2 diabetes have seen to be attenuated by Macitentan [16]. Moreover, data about the drug confirms the antitumor effect of the ETR antagonists, using the drug in combination with chemotherapy for treatment of ovarian tumors [17]. Likewise, Macitentan has shown potential in slowing down the dermal fibrotic processing in systemic sclerosis established via in vitro findings [18]. Although its preparations have a boxed warning to alert patients and healthcare providers that the drug can cause fatal toxicity to the developing embryo, therefore, it should not be used for pregnant women [5,6]. With respect to its advantages, Macitentan unlike other ETRAs has a dual ETA/ETB activity with enhanced potency and affinity to bind to ETA [14], which is more involved in the pathology of PAH [1]. It's less adversely affected and hinders liver [19] and bile salt transport system. It has an enhanced ETB receptor inhibition, a reinforced oral efficiency and an OD dosing in humans is backed by clinical studies. Furthermore, it is circulated in the endothelial system without hindrances [1,20].

Forthwith a combination of Macitentan with a compound having prostacyclin receptor (IP) agonist properties, concludes to a strong synergism for PAH and other treatments wherein endothelin is involved. Further, the apparent side effect related to the compounds having prostacyclin receptor (IP) agonist properties (e.g. Flushing or systemic hypotension) is observed to decline [15]. The pharmacokinetics dose adjustments of Macitentan in patients suffering from hepatic or renal impairment are extraneous. Drug–drug interactions are occulted [19], and one circulating pharmacologically active metabolite is omnipresent. The safety profile of Macitentan conceded superiority considering hepatic safety and edema/fluid retention compared with other drugs of the same class, and similar when considering the decrease in hemoglobin concentration. Macitentan attributes thus are appended and revolutionary important in the therapeutic long-term treatment of PAH [1,21,22].

Pulmonary Arterial Hypertension (pah)

PAH is a chronic, progressive life-threatening cardiovascular disorder in which patient experiences an abnormally high blood pressure in the arteries between the heart and lungs [23]. PAH, if remain untreated, can lead to right heart failure and ultimately death [7]. It is basically a disorder of the pulmonary vasculature that leads to the elevation of the mean pulmonary arterial pressure (mPAP). Different molecular and cellular mechanisms interact with each other and can lead to the development of PAH [20]. In PAH, survival rates are very low [7].

The term PAH was introduced at the World Health Organization (WHO) symposium on pulmonary hypertension in 1998. The first classification of pulmonary hypertension (PH) was given in 1973. Currently, PH is divided into five subgroups. PAH belongs to the group that includes idiopathic PAH, heritable PAH and PAH caused by factors such as connective tissue disease, HIV infection and congenital heart disease [7]. The new WHO classification is composed of four classes (**Table 1**) [20].

Table 1. World Health Organization functional classification of PAH [20].

Class	Symptoms
I	No dyspnea, chest pain, presyncope, or other interferences with usual physical activity
II	Usual physical activity causes dyspnea, chest pain, or presyncope
III	Less than usual activity causes dyspnea, chest pain, or presyncope
IV	Dyspnea and/or fatigue occur at rest. Presyncope may occur upon exertion.

PAH symptoms are non-specific and include dyspnea and fatigue, which usually develop during routine activity, right heart failure, diminished exercise ability and eventually reduced life expectancy [20]. In patients with PAH, shortness of breath and restrictions on the exercise ability is primarily results due to overload on the right side of the heart, which has to work harder than normal [5,23]. It also leads to initiation of i.v/s.c Prostanoids, lung transplantation, and/or atrial septostomy [21]. Epidemiologically PAH affects <1.8 in 10,000 people in the EU (fewer than 91,000 people) [24]. PAH is more prevalent in patients 50 years old and above, and more in females than males (23). Given the fact that PAH only affects one to two individuals per million people, it is very likely that such cases are easily misdiagnosed [7].

Echocardiography is an important diagnostic tool in the patients suffering from PH. It is diagnosed by catheterizing the right heart to measure mPAP. A normal map is in between (8-20 mmHg) at rest. A sustained elevation of mPAP above or equal to 25 mm Hg at rest or 30 mm Hg during exercise indicates the presence of PAH [20]. The European Society of Cardiology and the European Respiratory Society (ESC-ERS) guidelines have laid down very clear screening criteria for determining the presence of PH mainly based on tricuspid regurgitation peak velocity and systolic artery pressure (sPAP) [7-8].

Histologically, PAH is the formation of the plexiform lesion. Thickening of the plexiform lesion leads to vascular obstruction, which results in increased vascular resistance and induction of abnormal thrombosis [20]. Pathophisiologically (**Table 2**) targeting the endothelial system is a pharmacological strategy to slow down the progression of PAH. Endothelins (ET-1, ET-2, and ET-3) are autocrine or paracrine peptides known about their vasoconstriction properties. Endothelins are involved in multiple physiological activities such as blood pressure control, cellular apoptosis, remodeling of tissue's structures, fibrosis, and inflammation. Endothelin-1 (ET-1) is the dominant endothelin in the cardiovascular system. The receptors involved in mediating the endothelin system are ET_A and ET_B. Expression of ET_B in smooth muscle cells and endothelial cells causes vasoconstriction and vasodilation, respectively. However, expression of ET_A on smooth muscle cells produces vasoconstriction. ET-1 binds to ET_A and ET_B receptors on smooth muscle cells. ET_A is responsible for the pathological effects in PAH to a higher extent than ET_B [20].

Table 2. The common pathophysiological pathways that may be involved in the development of PAH [20].

Physiological Pathway	Pathological Alteration	Effect
Prostacyclin synthetase Nitric oxide synthetase	Reduced	Increased vasoconstriction, platelet activation, and vascular smooth muscle cells proliferation
Endothelin-1 peptide Thromboxane	Increased	Increased vasoconstriction and vascular smooth muscle cells proliferation
Vascular endothelial growth factor (VEGF) Platelet derived growth factor (PDGF)	Increased	Increased proliferation of smooth muscle cells, fibroblasts, and endothelial cells.

With respect to prognosis and treatment, over the past two decades, significant advances and progress have been made from understanding the pathophysiology of PAH to developments of treatment guidelines and new therapies [13]. Drugs developed for PAH target the three pathways (**Figure 1**) involved in the pathogenesis of PAH viz. Endothelin receptor antagonists (ERAs), prostacyclins and phosphodiesterase-5 inhibitors [7,8]. PAH drug therapy consists of specific as well as non-specific drugs such as oral anticoagulants, and diuretics. Diuretics remain an integral part of the PAH therapy because right heart failure leads to ascites and peripheral edema [7,8].

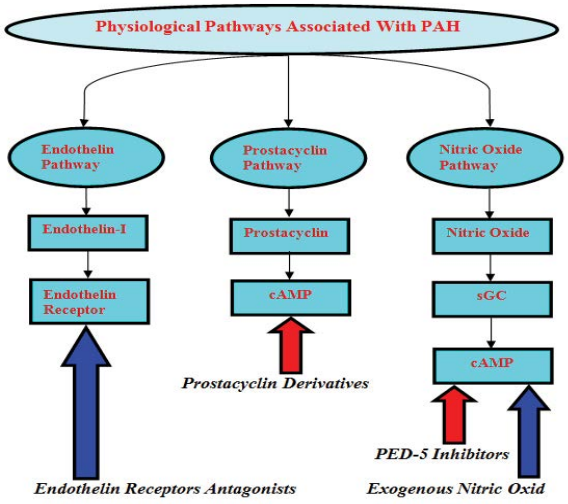


Figure 1. Three physiological pathways associated with PAH [7, 8].

Due to recent advances in PAH treatment, it is now possible to delay the progression of this disease compared to the symptomatic improvement in exercise tolerance a decade ago. Though there is no gold standard or evidence-based first-line treatment, the treatment choice is based on the patient's preference, the severity of the disease and the characteristics of the medication [20]. Unfortunately, the prognosis of PAH is very poor, and thus it is still incurable. However, there is ample evidence which prove that current PAH drugs used alone or in combinations, can significantly improve exercise ability, clinical symptoms, hemodynamics and even survival rate [13]. Despite of all these developments, there is a need for an early intervention, goal-oriented treatment and combination therapy to manage and treat this deadly disease. However, extensive research programs are going on to explore the existing and novel potent anti-proliferates therapies in search of new, safe and effective therapy of PAH. It is very much possible that in near future new agents or molecules targeting different and/or additional pathways is identified and become available clinically [13].

Prior to 2013, bosentan (Tracleer®) and ambrisentan (Letairis®) were the only two FDA-approved ETRAs for oral PAH treatment prior to the discovery and approval of Macitentan (Opsumit® by Actelion). The limiting factors of bosentan and ambrisentan use included hepatic injury, fluid retention, and hematological changes. Furthermore, phase III clinical trials of bosentan (EARLY trial) and ambrisentan (ARIES trial) were short-term and based their primary endpoints on exercise capacity using 6-MWD test rather

than decreasing morbidity and mortality as in Macitentan phase III clinical trial [9,20,21]. Macitentan is henceforth a new medication in the class of ETRA used for PAH treatment [6]. It offers many clinical advantages over other ERAs such as once daily dosing, fewer contraindications and use in patients with hepatic impairment [1,20].

History and Discovery

To begin with, an adventitious modification in the structure of bosentan (Tracleer®) (9) (an ERA used for treatment of PAH licensed in the US, the EU and other countries by Actelion Pharmaceuticals) lead to the development of alkyl sulfamide substituted pyrimidines (13) among which a random compound Macitentan (compound 17) interestingly stood out, conjuring to optimally improve in vivo efficacy [14], effective tolerability and a greater tissue penetration when compared to other ERA's [3].

Succinct look at development of Macitentan over the years

2003>Macitentan was selected for conducting preclinical studies.

2004>Entry-into Phase I

2005>Start of dose ranging Phase II study

2007>Phase III SERAPHIN study begins in PAH patients [21]

2012>SERAPHIN study meets its primary objective.

2013>US FDA approved the use of Opsumit 10 mg tablets in PAH [5,6].

Details of Trial and other relevant data in development of Macitentan

The Phase III study SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial hypertension to Improve clinical outcome) was aimed to evaluate the safety and efficacy of Macitentan through the primary endpoint of morbidity and all-cause mortality in patients with symptomatic PAH. A total of 742 patients enrolled from the worldwide, until December 2009 were randomized 1:1:1 to receive 3 mg and 10 mg doses of Macitentan once daily or placebo. Study results from 180 centers of North and South America, Europe, Asia-Pacific and Africa were available before the end of 2012 [21].

Aug 11: The PII MUSIC study in patients with idiopathic pulmonary fibrosis did not reach its primary efficacy endpoint. However, few new safety concerns were identified related to the 10 mg dose of Macitentan in patients treated for at least 14 months [25].

Feb 12: 120 deaths were reported in the SERAPHIN PIII study (n=740). The company said it was very unlikely the trial would show the drug extends life, but the results were expected Q2 2012 [10,21].

Apr 12: Initial analysis of the pivotal, long-term, event-driven SERAPHIN study suggested it had met its primary endpoint. Macitentan, at both the doses, 3 mg & 10 mg significantly decreased the risk of a morbidity/mortality event over the treatment period vs. placebo - by 45% in the 10 mg dose group ($p<0.0001$) & 30% in the 3mg gp ($p=0.0108$). A dose-dependent effect ($p<0.05$ for either dose) for secondary efficacy endpoints such as change from baseline to month 6 in six-minute walk-distance (MWD), change from baseline to month 6 in WHO functional class and time - over the whole treatment period - to either death due to PAH or hospitalization due to PAH was also observed. A 10 mg Macitentan was observed on all-cause mortality (p=ns) [9,10,21].

Oct 12: Chest published a meeting abstract of the PIII SERAPHIN study. The double-blind event-driven study, randomized 742 patients (≥12 years) with symptomatic PAH to placebo, Macitentan 3mg or 10mg, once daily. Stable background oral or inhaled PAH therapy was allowed. Mean treatment duration was 85.3, 99.5 and 103.9 weeks, respectively. Macitentan significantly decreased the risk of occurrence of morbidity and mortality events vs placebo (primary endpoint) by 30% in the 3mg group (97.5% CI:4-48%;P=0.0108) and 45% in the 10mg group (97.5% CI:24-61%; P<0.0001); this effect was irrespective of background PAH therapy (mainly phosphodiesterase type-5 inhibitors); risk reduction for Macitentan 3mg and 10mg was 17% (95% CI:-16-41%) and 38% (95% CI:11-57%) in the presence of background PAH therapy and 47% (95% CI:15-66%) and 55% (95% CI:28-72%) in the absence of background PAH therapy. Macitentan 3mg and 10mg also reduced the risk mortality due to PAH/ hospitalization by 33% (97.5% CI:3-54%; P=0.0146) and 50% (97.5% CI:25-67%; P<0.0001), respectively. Data on the six-minute walking distance and overall survival was not reported. Macitentan in general was well tolerated except few incidences of elevated liver aminotransferases and peripheral edema in all groups. Headache, nasopharyngitis and anemia were found to be the most frequently observed adverse effects of Macitentan [21].

NCT01847014 (SYMPHONY Extension) was an extension of AC-055-401, a multi-center, open-label, single-arm, a PIIIb study of 275 patients with PAH to psychometrically validate the PAH-SYMPACT instrument. The primary outcome was frequency of treatment-emergent adverse events, serious adverse events, marked laboratory abnormalities and adverse events leading to drug discontinuation in study from Baseline to Week 16.

Sep 13: Results of the SERAPHIN PIII study published in the N Engl J Med (2013; 369; 809). 742 patients symptomatic PAH were assigned to placebo, Macitentan 3mg or 10mg. The primary endpoints were 46%, 38% and 31% reduction respectively. Hazard ratios were 0.7 and 0.55 for 3 and 10 mg Macitentan vs placebo, respectively [21].

Oct 13: A subgroup analysis of SERAPHIN in treatment-naive patients presented at CHEST 2013. Macitentan 10mg reduced the risk of morbidity/mortality by 60% in incident patients (diagnosed shortly before entering the study) vs. placebo (HR 0.40, 95% CL 0.20-0.73); in prevalent patients (diagnosed more than six months prior entering on the study), Macitentan also reduced the risk of morbidity/mortality by 53% (HR 0.47, 95% CL 0.24-0.91). The risk reductions for the secondary endpoint of death due to PAH or hospitalization for PAH were 77% (HR 0.23, 95% CL 0.09-0.57) and 62% (HR 0.38, 95% CL 0.16-0.92) for incident and prevalent patients treated with Macitentan vs. placebo, respectively [21].

Details of clinical and preclinical studies

Preclinical studies consisted of *in vitro* animal studies of Macitentan. Assessments of inhibitory potency, receptor selectivity and expression of dual receptor antagonism of Macitentan were performed (i.e., inhibiting ETA and ETB); concluded in three and five times higher potency and selectivity compared to the other metabolites. The promising results of *in vitro*, analysis encouraged *in vivo* analysis in animals [20].

In a double-blind, randomized, placebo-controlled, single-ascending-dose entry-into-humans study (Phase I), researchers investigated the tolerability, pharmacodynamics, and pharmacokinetics of ascending single doses in healthy male subjects (56 in seven groups). Unlike other ETRAs, Macitentan did not inhibit human hepatic transporters and had no effect on the serum total concentration of bile salts, which might eliminate the possibility of inducing hepatic toxicity and cholestasis, respectively. The investigators identified a major active metabolite of Macitentan, ACT-1325779 ($t_{1/2}$ lower than Macitentan), in the plasma similar to what was found in animal studies [20].

Further the long half-life of Macitentan in addition to the long duration of action (40 hours) apparent in animal studies, gave way to OD dose in succeeding clinical trials. A double-blind, placebo-controlled, multiple-ascending-dose study (Phase II) was performed to evaluate the safety profile of Macitentan, including its interactions with CYP3A4 and effects on liver enzymes. Single daily doses of 1,3,10 and 30 mg Macitentan was administered for ten days in 32 healthy male subjects. Macitentan appeared to be well tolerated with no side effects among all except headache. On day 11, asymptomatic mild elevation of AST and ALT between Macitentan and placebo implied safety profile better than previously studied ETRA's [20].

Additionally, based on phase I and phase II clinical trial results, a dose of 10 mg daily was identified to be used for the phase III clinical trial, and pharmacodynamics and pharmacokinetic properties of Macitentan were looked upon [20].

Phase III clinical trial of Macitentan, SERAPHIN trial [21] was then initiated. It was a multicenter, double-blind, randomized, placebo-controlled and event-driven phase III trial. Morbidity and mortality of Macitentan were assessed in 742 patients randomly assigned in a 1:1:1 ratio to placebo, 3 mg, and 10 mg once daily. Participants were 12 years of age and older, diagnosed with idiopathic or PAH (57%, confirmed by right heart catheterization), related to connective-tissue disease (31%), repaired congenital systemic-to-pulmonary shunts (8%), HIV, or drug use or toxin exposure. Patients had to fall in class II, III, and IV PAH (WHO). Patients who were on intravenous (IV) or subcutaneous (SC) prostanoids were excluded to avoid masking the nuances of ETRA's. Death and worsening PAH symptoms were initial outcomes (**Tables 3-5**) [20,21]. At least 15% reduction from baseline of the 6-MWD was observed. The results were further confirmed with a second 6-minute walk test performed on a different day within two weeks of the first test [9].

Table 3. The primary endpoint of worsening of PAH [20, 21].

Macitentan vs. Placebo	Hazard ratio (worsening of PAH)	Confidence interval (97.5%)	p	P
3 mg vs. placebo	0.67	0.52-0.96	0.01	0.01
10 mg vs. placebo	0.50	0.39-0.76	0.001	0.001

Table 4. The primary endpoint of death [20, 21].

Macitentan vs. Placebo	Hazard ratio of composite endpoint of death	Confidence interval (97.5%)	P
3 mg vs. Placebo	0.67	0.46-0.97	0.01
10 mg vs. placebo	0.50	0.34-0.75	0.001

Table 5. Secondary endpoint of 6-MWD at 6-months [20, 21].

Group	6-MWD mean increase/decrease	Treatment vs. Placebo (97.5% CI)	P
Placebo	-9.4 m	-	-
3 mg	+7.4 m	16.8 m (-2.7-36.4)	0.01
10 mg	+12.5 m	22.0 m (3.2-40.8)	0.008

PAH symptoms worsening included at least one of the following:

- Higher WHO PAH functional class
- No change from baseline in patients with WHO PAH class IV
- Signs of right heart failure worsened; the patient did not respond to oral diuretic therapy.
- Additional PAH treatment needed [20] .

Event-driven studies funded by Actelion Pharmaceuticals were also performed; SERAPHIN ClinicalTrials.gov number, NCT00660179 [21], concluded that Macitentan decimates morbidity and mortality among patients with PAH; simultaneous reduce the risk of PAH-related death or hospitalization. The long term SERAPHIN OL clinical trial further evaluated the long-term safety and tolerability of Macitentan in PAH patients. Finally, a total of 287 patients had a primary endpoint event over a period of 115 weeks. Patients who were taking 3 mg or 10 mg Macitentan had statistically better clinical outcomes than patients who were treated with placebo [6,20].

FDA guidelines

Opsumit carries a boxed warning to alert patients and health care professionals that the drug should not be used for pregnant women as it can harm the developing fetus 6 (21). Female patients can receive the drug only through the Opsumit Risk Evaluation and Mitigation Strategy (REMS) program [23,25]. This restricted-distribution program requires prescribers to be certified by enrolling in the program; all female patients to be enrolled under the program and comply with applicable pregnancy testing and contraception requirements before starting the treatment; and pharmacies to be certified and to dispense Opsumit only to patients who are authorized to receive it. Efficacy of Macitentan 10 mg on the primary endpoint is well established across subgroups of age, sex, ethnic origin, geographical region, etiology, by monotherapy or in combination with another PAH therapy and by WHO FC (I/II and III/IV). The most commonly reported adverse drug reactions are nasopharyngitis (14.0%), headache (13.6%) and anemia (13.2%) sore throat, bronchitis, headache, flu and urinary tract infection. The majority of adverse reactions are mild to moderate in intensity [5,23].

FDA approval

On October 2012, Actelion submitted a new drug application to the US FDA seeking approval for Macitentan (Opsumit®) in PAH patients [3]. Oral Macitentan 10 mg once daily, obtained U.S. Food and Drug Administration (FDA) approval on October 13, 2013; Trailed next by Canada [3]. Opsumit is now marketed by San Francisco-based Actelion Pharmaceuticals US [5].

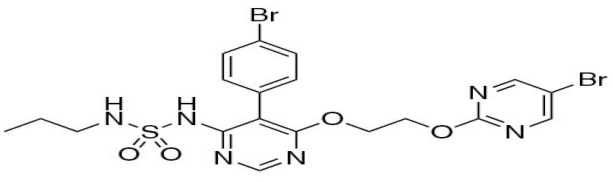
On 22nd November 2012, Actelion confirmed that it had applied for Market Authorization Application (MAA) to the European Medicines Agency (EMA), and a validation letter had been received and is being pursued by EU [3], from the Committee for Medicinal Products for Human Use for the treatment of PAH; furthermore, it is under regulatory review of several other countries across the globe (Switzerland, Australia, Taiwan and Mexico) for the treatment of the later [3,26].

Future Aspects

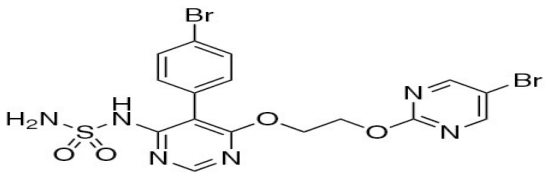
Macitentan is currently being studied in the multi-center, double-blind, randomized, placebo-controlled, parallel-group Phase III study MAESTRO (Macitentan in Eisenmenger Syndrome to Restore exercise capacity) to evaluate the effects of Macitentan on exercise capacity in subjects with Eisenmenger Syndrome. In this ongoing study, approximately 220 subjects are randomized in a 1:1 ratio into 2 treatment groups (Macitentan 10 mg or placebo) over a 16-weeks treatment period. Following excellent preclinical results, a Phase I/Ib open-label study has been initiated with Macitentan in patients with recurring glioblastoma. Actelion is also hoping to extend it's a synergistic PAH franchise with selexipag, an IP receptor agonist in phase III testing. Results from the main GRIPHON trial are due to be out in the 2014 [5,6,27].

Physiochemical Properties

Systematic (IUPAC) name of Macitentan is N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propylsulfamide OR Sulfamide, N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-propyl-amine (**Figure 2**).One of the metabolites of Macitentan is also pharmacologically active at the ET receptors and is estimated to be about 20% as potent as the parent drug *in vitro* [6,28].



Macitentan



ACT-132577

Figure 2. Chemical structure of Macitentan and its active metabolite (ACT-132577).

Macitentan is a stable crystalline powder, non-hygroscopic, insoluble in water and not light sensitive. It should be stored in a close container, at room temperature, away from heat, moisture, and direct light [5,23]. It should not to be frozen and kept out of reach of children. To be disposed off as indicated on the label. A 10 mg tablet is priced to $ 3.08 [29].

The dissolution profile points to a rapid disintegration of all formulations with >90% dissolution of Macitentan within 45 minutes. Bioequivalence criteria meet for AUC_0-t and AUC_0-∞. Mean C_{max} for tablet was 19% lower compared to capsules with its lower 90% confidence limit below the accepted bioequivalence range [28,30].

Distribution Coefficient (Log D)

Log D of Macitentan between n-octanol and aqueous phosphate buffer, pH 7.4, determined in duplicates was found to be 800:1 [1]. It is markedly less prone to drug–drug interactions than other ERA's due to its low plasma concentrations and a minimal accumulation within the liver (**Table 6**) [19].

Table 6. Physicochemical parameters of Macitentan [19]

Property	Value
Distribution Coefficient D (*n*-Octanol/Aqueous Buffer)	800:1
Log D	2.9
Nonionized Form (at pH 7.4)	6%
State	Solid
Water solubility	6.68e-03g/l (Insoluble)
logP	3.05
logP	3.69
logS	-4.9
pKa (strongest acidic)	7.76
pKa (strongest basic)	2.26
Physiological charge	0
Hydrogen acceptor count	9
Hydrogen donor count	2
Polar surface area	128.22
Rotatable bond count	9
Refractivity	126.98
Polarizability	50.55
Number of rings	3
Bioavailability	1
Rule of five	No
Ghose filter	No
Veber's rule	No
MDDR-like rule	Yes

Commercial dosage form (OPSUMIT)

Macitentan 10 mg (Film-coated tablet. 5.5 mm, round, biconvex, white to off-white, film-coated tablets, debossed with "10" on one side) [5].It contains excepients like 37 mg of lactose (as monohydrate), approximately 0.06 mg of lecithin (soya) (E322) Microcrystalline cellulose (E460i), Sodium starch glycolate Type A Povidone, Magnesium stearate (E572), Polysorbate 80 (E433) Film coat, Polyvinyl alcohol (E1203), Titanium dioxide (E171), Talc (E553b), Xanthan gum (E415), etc. [5].

Incompatibilities

Not applicable.

Shelf life

3 years

Special precautions for storage

Do not store above 30°C.

Nature and contents of the container

White, opaque PVC/PE/PVdC/Aluminium foil blisters in cartons containing 15 or 30 film-coated tablets. White high-density polyethylene bottles with a silica gel desiccant, in cartons containing 30 film-coated tablets (3).

Pharmacokinetics

Macitentan on oxidative depopulation produces an active metabolite, ACT-132577. Both Macitentan and ACT-132577 are excreted [31] via urine (about 2/3 of all metabolites) and feces (1/3) (4,5) (**Table 7**) [6]. Broadly Macitentan is slowly absorbed and,

at a dose of 300 mg, the $t_{1/2}$ were 17.5 h. The dose-proportionality coefficient β for C_{max} (95% CI) was 0.83 indicating less than dose-proportional pharmacokinetics of Macitentan. In plasma, a pharmacologically active oxidative depropyl metabolite, ACT-132577 was found, whereas in urine two minor metabolites detected. The $t_{1/2}$ of ACT-132577 (95% CI) is 65.6 h (53.1). Macitentan dose-dependently increased endothelin-1 concentrations up to 2.2-fold (95% CI) at a dose of 600 mg, but no consistent effect on total bile salts [32]. Macitentan is well tolerated up to doses of 300 mg. The maximum tolerated dose. Headache, nausea and vomiting are dose-limiting adverse events [6].

Table 7. Pharmacokinetics profiling of Macitentan [6]

Property	Value
Half-life	16 hours
Peak plasma concentration time	Reached after 8 hours
Binding to plasma proteins	99% bound to plasma proteins, mainly albumin.
Volume of distribution	50 L
Metabolism	It metabolized primarily by CYP3A4.
Elimination	50% in urine and 24% in feces
Renal impairment CrCl (15-29 ml/min)	Increased by 30% and 60% respectively. The increases are not considered clinically significant.
Hepatic impairment	Decreased exposure in mild, moderate, or severe hepatic impairment. However, the decrease is not clinically significant.

VARIOUS STUDIES ON MACITENTAN

mRNA level induction quantification by real-time RT-PCR in LS180 cells revealed that Macitentan significantly induced mRNA expression of cytochrome P450 3A4 (*CYP3A4*), *P*-glycoprotein (*P*-gp, *ABCB1*), solute carrier of organic anions 1B1 (*SLCO1B1*), and uridinediphosphate-glucuronosyltransferase 1A3 (*UGT1A9*). By a reporter gene assay, Macitentan was established as a potent activator of pregnane X receptor (PXR). Using the transporter over-expressing cell lines and fluorescent specific substrates of the respective transporters, evaluation of drug transporters was performed revealing Macitentan as an inhibitor of *P*-gp, breast cancer resistance protein (BCRP), SLCO1B1, and SLCO1B3. Macitentan was demonstrated to be a moderate inhibitor of CYP3A4 and CYP2C19 using commercial kits. After administering a single oral dose of 10 mg Macitentan, the pharmacokinetic parameters, including area under the curve from zero to infinity (AUC_{∞}) were derived from plasma concentration–time profiles [19]. There is no need to adjust the Macitentan dose in patients with hepatic or renal function impairment as pharmacokinetics alterations of Macitentan are not considered clinically relevant [33,34].

In a study of the disposition and metabolism of Macitentan (14) by a single oral 10 mg dose administration of C-Macitentan to six healthy male subjects, radioactivity in matrices was determined using a liquid scintillation counter. The mean (± SD) cumulative recovery of radioactivity from feces and urine was found to be 73.6% (± 6.2%) of the administered radioactive dose, with 49.7% (± 3.9%) cumulative recovery of urine, and 23.9% (± 4.8%) from feces. The proposed structure of metabolites was based on mass spectrometry characteristics and, when available, confirmed by comparison with reference compounds ACT-132577 (in the urine, mainly), and the carboxylic acid metabolite ACT-373898 (in faeces, mainly) were identified. Concentrations of total radioactivity in whole blood were lower as compared to plasma. These results indicated that Macitentan and its metabolites poorly bind to or penetrate into erythrocytes [31,33,34].

MACITENTAN METABOLITE (ACT 132577) AND ITS STUDIES

In this single-center, open-label study, 10 healthy subjects of each ethnic origin with a male/female ratio of 1:1 in each group were administered a single oral 10-mg dose of Macitentan. Blood samples were taken to determine plasma levels of Macitentan and its active metabolite, ACT-132577. The safety and tolerability were monitored using standard assessments (**Table 8**) [30,31].

Table 8. The difference between pharmacokinetics of Macitentan and its metabolite (ACT-132577) [30,31]

Name of drug	Half-life (hours)	Day, at which steady state was reached.	Volume of Distribution
ACT-132577	48	Day #7	40 L
Macitentan	16	Day #3	50 L

For both Macitentan and its metabolite, females had an approximately 15% higher exposure to ACT-132577 than male subjects. ACT-132577 (metabolite with lower potency), had a half-life of about 48hours and accumulated approximately 8.5-folds. Plasma concentration–time profiles for Macitentan and ACT-132577 (active) were found to be similar in healthy subjects and subjects with hepatic SRFI [30,34].

PHARMACOKINETICS PROFILE OF MACITENTAN

Absorption

Maximum plasma concentrations of Macitentan reached in 8 hours after administration. The absolute bioavailability after

oral administration is not known. Thereafter, plasma concentrations of Macitentan and its active metabolite decrease slowly, with an apparent elimination half-life of approximately 16 hours and 48 hours, respectively. In healthy subjects, food does not interfere with the absorption; therefore, Macitentan may be taken with or without food [6,33].

Distribution

Macitentan and its active metabolite are highly bound to plasma proteins (> 99%), primarily to albumin and to a lesser extent to alpha1-acid glycoprotein. Both are well distributed into tissues as indicated by an apparent volume of distribution (Vss/F) of approximately 50 L and 40 L for Macitentan and ACT-132577, respectively [6].

Metabolism

Macitentan undergoes four primary metabolic pathways. Oxidative depropylation of the sulfamide yields a pharmacologically active metabolite. This biotransformation is cytochrome P450 dependent, mainly CYP3A4 (approximately 99%) with minor contributions of CYP2C8, CYP2C9 and CYP2C19. The active metabolite circulates in human plasma and may contribute to the pharmacological effect. Other metabolic pathways yield pharmacologically inactive products. Several members of the CYP2C family, namely CYP2C8, CYP2C9 and CYP2C19, as well as CYP3A4, are involved in the formation of these metabolites [6,31].

Elimination

Macitentan is only excreted after extensive metabolism. The major excretion route is via the urine, accounting for about 50% of the dose [6].

Special populations

There is no clinically relevant effect of age, sex or ethnic origin on the pharmacokinetics of Macitentan and its active metabolite [5].

Renal impairment

Exposure to Macitentan (CrCl 15-29 mL/min) and its active metabolite was increased by 1.3-(60%) and 1.6-(30%) fold, respectively, in patients with severe renal impairment. Though, this increase is not considered clinically relevant [34].

Hepatic impairment

Exposure to Macitentan was decreased by 21%, 34%, and 6% and, for the active metabolite by 20%, 25%, and 25% in subjects with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, and C), respectively. This decrease is not considered clinically relevant. Other ERAs also cause elevations of aminotransferases, hepatotoxicity, and liver failure [6,34].

Pregnancy

Macitentan may cause fetal harm when administered to a pregnant woman. Macitentan is contraindicated in females who are pregnant [6].

Hemoglobin Decrease

Macitentan and other ERA's cause a decrease in hemoglobin concentration and hematocrit. These decrease occurred early and stabilized thereafter. Initiation of Macitentan is not recommended in patients with severe anemia. It is recommended to check hemoglobin prior to initiation of treatment and reverberations during treatment [6].

Interaction with an enzyme Inducers/Inhibitors

The drug is metabolized by CYP3A4, a liver enzyme. Strong CYP3A4 inducers such as rifampin significantly reduce Macitentan exposure (decreases the AUC of the drug's blood plasma concentration by 79%) whereas the concomitant use of strong CYP3A4 inhibitors like ketoconazole approximately doubles Macitentan exposure. Many HIV drugs like ritonavir (CHEMBL163) are strong inhibitors of CYP3A4 [6]. Co-administration of cyclosporine has only a slight effect on the concentrations of Macitentan and its active metabolite [31].

PHARMACOLOGY

Endothelin receptors are found in the endothelial cells of blood vessels and smooth muscle. Macitentan antagonizes/blocks endothelin receptors, by binding to the receptors, endothelin A and B (ETA and ETB), preventing the agonist endothelin-1 (ET-1) from binding and stimulating the ETA and ETB receptors [6].

Mechanism of Action

Macitentan is an endothelin receptor antagonist (ETA) that prevents binding of ET-1 to both ET-A and ET-B receptor with high affinity and sustained occupancy to ET receptors in pulmonary arterial smooth muscle cells. One of its metabolites, although 20% potent, is also active in ET system. Endothelin (ET) -1 and its receptors (ETA and ETB) mediate a variety of deleterious effects, such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation [6]. In disease conditions such as PAH, the local ET system is up regulated and beneficially effects vascular hypertrophy and in organ damage [5].

PHARMACODYNAMICS

Macitentan is an orally active, potent dual endothelial receptor antagonist (ERAs) which is active on both endothelial A (ETA) and endothelial B (ETB) receptors. The selectivity of Macitentan for ETA is 100 fold more than ETB *in vitro* (1). Macitentan inhibits the binding of endothelin (ET) -1 to both ETA and ETB receptors. Thus, it prevents the endothelin mediated activation of the second messenger system that results in vasoconstriction and smooth muscle cell proliferation [20,33]. Macitentan shows a dose-dependent increase in the plasma concentration of endothelin (ET) -1. The increase is due to the blockade of ETB receptors, which are responsible for the clearance of ET-1 at the level of lung. Macitentan and its active metabolite (ACT-132577) are 50-fold and 16-fold respectively more selective for ETA receptors than for the ETB receptors [5,6].

Pulmonary Hemodynamics studies

The clinical efficacy study in patients with PAH was assessed with hemodynamic parameters in patients after six months of treatment. Patients treated with 10 mg (N=57) compared to placebo (N=67), achieved a median reduction of 37% (95% CI 22-49) in pulmonary vascular resistance and an increase of 0.6 L/min/m^2 (95% CI 0.3-0.9) in the cardiac index.

Cardiac Electrophysiology studies

In a randomized, placebo-controlled four-way crossover study with a positive control in healthy subjects, repeated doses of Macitentan 10 and 30 mg (three times the recommended dosage) had no significant effect on the QTc interval [5,6,35].

THERAPEUTIC CONSIDERATIONS

Macitentan treats symptoms of PAH, characterized by high blood pressure in the main artery that carries blood from the right side of the heart (the ventricle) to the lungs. When small blood vessels of lung show resistance to blood flow, the right ventricle is bound to work harder to pump enough blood through the lungs. Macitentan thereby relaxes these blood vessels and increased the supply of blood to the lungs, thereby reducing the heart's workload [23].

The combination of Macitentan and its major metabolite reduces the levels of SMA after 48 h in scleroderma fibroblasts with symptoms of lesional skin (26). Studies show that ovarian cancer cells [17], multidrug resistant, expressed by the endothelin axis, are precisely sensitive to treatment with a dual ET antagonist and can be resensitized to both Taxol and cisplatinum. This combined therapy shows a significant reduction in tumor demerits [17].

It is emerging as a novel agent in the treatment of cardiovascular disorders associated with chronic tissue ET system activation (viz. Heart failure, angina pectoris, pulmonary and systemic hypertension and erectile dysfunction) [15]. Experiments have confirmed that the ET system plays a significant role in the pathogenesis of chronic complications in type-2 diabetes. Such diabetes induced changes can be reduced by Macitentan therapy [16].

POSOLOGY AND ADMINISTRATION

Dosage Form & Strength

Macitnetan (OPSUMIT®) may be administered orally with or without food and the recommended dose of Macitentan as per the clinical findings is 10mg once daily. The drug should be taken every day at the same time. If the patient misses a dose of the drug, it should be taken as soon as possible, and then the next dose should be taken regularly at the scheduled time. Double dose at the same time should be avoided if a dose of the drug has been missed. It is indicated for the treatment of PAH (WHO Group, I) to delay disease progression [5].

The drug should be used with caution in elderly patients above 65 years of age. Also, no adjustment is required for the patients with hepatic or renal impairment based on the pharmacokinetics data. The drug is not recommended in patients undergoing dialysis. Moreover, the clinical safety and efficacy of Macitentan have not been established in pediatric population [5,6].

Dosage Modifications

Pediatric: Appropriate studies of safety and efficacy establishment have not been performed on the relationship of age to the effects of Macitentan in the pediatric population [20].

Geriatric: Appropriate studies performed to date have not demonstrated geriatric-specific problems that would limit the usefulness of Macitentan in the elderly. However, no dose adjustment is required in patients over the age of 65 years. There is limited clinical experience in patients over the age of 75 years. Therefore, Macitentan should be used with caution in this population [23].

Renal impairment: In case of Severe (CrCl 15-29 mL/min), No dosage modification is needed. Based on PK data, no dose adjustment is required in patients with renal impairment [23].

Hepatic impairment: In cases of mild, moderate, or severe (Child-Pugh Class A, B, and C): No dosage modification is needed. However, there is no clinical experience with the use of Macitentan in PAH patients with moderate or severe hepatic impairment. Macitentan must not be initiated in patients with severe hepatic impairment [5,6,23,35].

The drug increases the Aminotransferases level (greater than three times the Upper Limit of Normal (> 3 × ULN), on 10 mg OD dosing (**Table 9**).

Table 9. Incidence of elevated aminotransferases in SERAPHIN studies [35]

Elevated Aminotransferases	Macitentan10 mg	Placebo
>3 x ULN	3.4%	4.5%
>8 x ULN	2.1%	0.4%

Overdose: Serious adverse reactions such as nausea, headache, vomiting was observed in healthy volunteers who received a single dose of 600 mg of OPSUMIT® (60 times the initial approved dose). Therefore, supportive measures must be taken in case of overdose of the drug. Dialysis is unlikely to be effective due to a high degree of protein binding of Macitentan [5,6,35].

CLINICAL EFFICACY AND SAFETY

The clinical efficacy and safety of Macitentan were assessed using a primary end point of morbidity and mortality in long-term trials (SERAPHIN) discussed earlier in the paper. All the worsening events in the study were confirmed by an independent adjudication committee, blinded to treatment allocation [5,21]. Safety studies involving treatment with Macitentan (10 mg) showed an improvement of at least one WHO functional class at month 6 in 22% patients when compared to 13% patients treated with placebo. All these time-to-event endpoints were estimated by Kaplan-Meier method and analyzed by log-rank test. A sensitivity analysis performed to account for premature discontinuation of treatment was consistent with primary analysis. Macitentan significantly reduced the morbidity and mortality among patients with symptomatic PAH [26,36].

ADVERSE REACTIONS

Based on the clinical study of Macitentan, the most commonly observed adverse reactions are nasopharyngitis (14%), Bronchitis 12%, Anemia 13%, headache (13.6%), anemia (13.2%), bronchitis (12%), influenza (6%) and UTI (9%). Most of the adverse reactions are mild to moderate in intensity [21,23]. More common adverse symptoms include pale skin, difficulty in breathing on exertion, unusual bleeding or bruising, tiredness or weakness. Fewer common ones are, Abdominal or stomach pain or tenderness; clay colored stools, dark urine, difficult, burning, or painful urination, frequent urge to urinate, lower back or side pain, muscle aches, difficulty with breathing, tightness in the chest, yellow eyes or skin [23,32].

Hypotension has also been reported with the use of 10 mg Macitentan for 7.0% patients with PAH in a long-term double-blind study as compared to 4.4% on a placebo. This relates to 3.5events/100 patient-years on Macitentan 10mg, compared to 2.7events/100 patients-years on placebo. Edema/fluid retention has also been reported with the use of Macitentan, which is also a clinical manifestation of right heart failure and underlying PAH disease [23]. Some side effects may occur that usually do not need medical attention and usually these side effects may go away during treatment as the body adjusts to the medicine [5,6,23,35].

DRUG-INTERACTIONS

Macitentan might react with the following medicines. Therefore, the concurrent use of either of these with macitentan is not recommended. However, if the clinical condition demands, the prescriber may change the dose of the drug or timing of drug administration [23]. The drugs which interact with Macitentan include; boceprevir, bosentan, carbamazepine, clarithromycin, conivaptan, dabrafenib, darunavir, delavirdine, dexamethasone, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir, eslicarbazepine, etravirine, fosamprenavir, imatinib, indinavir, isoniazid, ketoconazole, lopinavir, nafcillin, nelfinavir, nevirapine, nicardipine, oxcarbazepine, pentobarbital, posaconazole, primidone, quinidine, rifapentine, ritonavir, telithromycin, tipranavir, voriconazole, mitotane, sildenafil, atazanavir, cobicistat, enzalutamide, fosphenytoin, itraconazole, nefazodone, phenobarbital, phenytoin, rifabutin, rifampin, saquinavir, St John's Wort, tipranavir, etc. [5,6,23].

In-vitro studies

Macitentan is metabolized by the cytochrome P450 enzymes, mainly CYP3A4, CYP2C8, CYP2C19. Macitentan at 10 mg once a day dose does not show any inhibitory or inducing effects on cytochrome P450 enzymes. Furthermore, it is neither a substrate nor an inhibitor of the multi-drug resistance protein (P-gp, MDR-1).

Macitentan or its active metabolite (ACT-132577) do not inhibit the hepatic or renal uptake transporters viz. Organic anion transporting polypeptides (OATP1B1) and (OATP1B3) at clinically relevant concentrations. Macitentan and/or its active metabolite are not the substrate of the transporting polypeptide but enter the liver by passive diffusion. It also does not interact with the bile salt export pump (BSEP) and the Na-dependent taurocholate co-transporting polypeptide (NTCP) [5,19,35]. Macitentan and its metabolite also inhibit the breast cancer resistance protein (BCRD) at normal dosing.

In-vivo studies

Drug interactions of Macitentan and its active metabolite have been studied only in healthy adults [36].

Warfarin: (avoid) Macitentan administered at multiple doses of 10 mg once daily had no significant effect on exposure to

S-Warfarin (CYP2C9 substrate) or R-Warafarin (CYP3A4 substrate) after a single dose of 25 mg warfarin. Macitentan had no effect on the pharmacodynamics of warfarin on the International Normalized Ratio (INR). Furthermore, warfare had no effect on the pharmacokinetics of Macitentan and its active metabolite (ACT-132577).

Sildenafil: (no dose adjustment needed) The exposure to the sildenafil 20 mg t.i.d was increased by 15% during the concomitant administration of Macitentan at 10mg once daily. The pharmacokinetics of Macitentan were unaffected by sildenafil, a CYP3A4 substrate while there was a reduction by 15% in the exposure to the active metabolite of Macitentan (ACT-132577). All these changes are not clinically relevant and the safety and efficacy of Macitentan in combination with sildenafil were determined in a placebo-controlled trial in patients with pulmonary arterial hypertension (PAH) [37].

Ketoconazole: (avoid) There is a 2-fold approximately increased exposure to Macitentan in the presence of ketoconazole 400 mg once daily, which is a strong CYP3A4 inhibitor. However, the increase was approx. 3-fold in the presence of ketoconazole 200 mg twice daily using physiologically based pharmacokinetic (PBPK) model. There was a reduction in exposure by 26% of the active metabolite of Macitentan. Precaution must be taken when Macitentan is administered concomitantly with strong CYP3A4 inhibitors.

Cyclosporine A: (no dose adjustment required) Concomitant treatment by Macitentan with cyclosporine A 10 mg b.i.d., had no effect on the steady-state exposure to Macitentan and its active metabolite (ACT-132577).

Strong CYP3A4 inducers (avoid): Rifampicin, a potent inducer of CYP3A4, reduced the steady-state exposure to Macitentan by 79%, but, had no effect on the exposure to its active metabolite. There was a reduction in the efficacy of Macitentan in the presence of potent inducer of CYP3A4 such as rifampicin. Thus, the combination of Macitentan with such an inducer should be avoided.

Hormonal contraceptives: Although specific drug-drug interaction studies with hormonal contraceptives have not been confirmed, Macitentan did not affect the exposure to other CYP3A4 substrates such as sildenafil. Therefore, no reduced efficacy of hormonal contraceptives is expected [5,20,35].

CONTRAINDICATIONS, SAFETY & TOLERABILITY

Allergies

The healthcare professional must be informed of the complete history of patients, if any types of allergies, such as to foods, dyes, preservatives, or animals, or any other unusual allergies have previously struck the patient. These might interfere with Macitentan therapy [23].

Black Box Warnings

Pregnancy: Macitentan is contraindicated in females who are pregnant and also in women of childbearing potential who are not using reliable contraception as it is associated with fetal toxicity in a pregnant woman.

Pregnancy Category: X; It produces teratogenic effects when administered to animals. Macitentan might likely produce serious birth defects if used by pregnant women.

Use in women of childbearing potential: Macitentan treatment should only be initiated in women of childbearing potential when the absence of pregnancy has been verified. Women should not become pregnant for one month after discontinuation. Monthly pregnancy tests during treatment with Macitentan are recommended to allow the early detection of pregnancy [35-38].

Studies: In both rabbits and rats, there were cardiovascular and mandibular arch fusion abnormalities; administration to female rats from late pregnancy through lactation caused reduced pup survival and impairment of the male fertility of the offspring at all dose levels tested [25].

Breastfeeding: There are no data available, whether Macitentan is excreted in human breast milk. Macitentan and its metabolite were found to be present in the milk of lactating rats. At the risk of the breastfeeding child should not be excluded. Macitentan is, therefore, contraindicated during breastfeeding [5,6].

Male fertility

The development of testicular tubular atrophy in male animals was observed in many studies after treatment with Macitentan. The relevance of this finding to humans is unknown, but a deterioration of spermatogenesis and deterioration of sperm count was not excluded.

Studies: Impairment of Fertility: Treatment of juvenile rats from postnatal Day 4 to Day 114 led to reduced body weight gain and testicular tubular atrophy at exposures 7-fold the human exposure.

Fertility was not affected

Reversible testicular tubular dilatation was observed in chronic toxicity studies at exposures greater than 7-fold and 23-

fold the human exposure in rats and dogs, respectively. After 2 years of treatment, tubular atrophy was seen in rats at 4-fold the human exposure. Macitentan did not affect male or female fertility at exposures ranging from 19- to 44-fold the human exposure, respectively, and had no effect on sperm count, motility, and morphology in male rats. No Testicular findings were noted in mice after treatment up to two years [5,6,35].

Animal Toxicology

In dogs, Macitentan decreased blood pressure at exposures similar to the therapeutic human exposure. Intimal thickening of the coronary arteries was observed at 17-fold the human exposure after 4 to 39 weeks of treatment. Due to the species-specific sensitivity and the safety margin, this finding was considered not relevant to humans. There were no adverse liver findings in long-term studies conducted in mice, rats, and dogs at exposures of 12- to 116-fold the human exposure [5,6,35].

Effects on the ability to drive and use machines

Macitentan has shown to have a minor influence on the ability to drive and use machines. The clinical status of the patient and the adverse reaction profile of Macitentan (such as headache, hypotension) should be kept in mind when considering the patient's ability to drive and use machines [5,6,35].

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the drug effect is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are informed in the Macitentan leaflet to report any suspected adverse reactions via the national reporting system [5,6,35].

Laboratory abnormalities (From SERAPHIN studies)

Hemoglobin: Macitentan 10 mg caused a mean decrease in hemoglobin versus placebo of 1 g/dL in a double-blind study in PAH patients. Approximately 8.7% of patients showed a decrease in hemoglobin concentration to below 10 g/dL as compared to 3.4% of placebo-treated patients.

White blood cells: Macitentan 10 mg caused a decrease in mean leukocyte count from baseline of 0.7 × 109/L, however, no change was observed in placebo-treated patients.

Platelets: Macitentan 10 mg is also associated with a decrease in mean platelet count of 17 × 109/L, versus a mean decrease of 11 × 109/L in placebo-treated patients.

Edema/fluid retention: Regular use of ERAs cause edema and is also a clinical symptom of right heart failure and underlying PAH disease. The incidence of edema in the Macitentan 10 mg and placebo treatment groups were 11.0 events / 100 patient-years and 12.5 events / 100 patient-years respectively [5,6,35].

Other Medical indications

The presence of other medical problems may affect the use of Macitentan. Macitentan may worsen the anemia or severe liver diseases. Macitentan tablet, must be swallowed whole, not crushed, broken, or chewed. It is also subject to a restricted distribution program. Macitentan comes with an extra patient information sheet called a Medication Guide. Because, it is associated with decreased hemoglobin and hematocrit concentrations; the therapy with ERAs is not recommended if severe anemia is present. If pulmonary edema occurs, consider the possibility of associated pulmonary veno-occlusive disease, and if confirmed, discontinue concurrent administration and its use should be avoided with strong CYP3A4 inhibitors [5,6,23,35].

CONCLUSION

Macitentan, as witnessed in the above discussion, is an orphan, new and better medication belonging to ETRA class for PAH treatment. In contrast to other ETRA's, it has prolonged receptor binding properties and a greater tissue penetration; it possesses fewer contraindications but possesses better hepatic safety and is used once daily only [38]. Macitentan significantly reduces the risk of death due to PAH or hospitalization for PAH. It is further substantiated that Macitentan can be seen as revolutionary drug, important in the therapeutic long-term treatment and a better alternative remedy for PAH-related outcomes.

CONFLICT OF INTEREST STATEMENT

None

ABBREVIATIONS

US FDA: United States Food and Drug Administration; ET/ERA's/ETRA's: Endothilin Receptor Antagonists; PAH: Pulmonary Arterial Hypertension; WHO FC: World Health Organization Functional Class; CVS: Cardio Vascular System; MWD: Minute Walk Distance; OD: Once Daily; IUPAC: The International Union of Pure and Applied Chemistry; IPF: Idiopathic Pulmonary Fibrosis; HIV: Human Immunodeficiency Virus area under the curve relative and infinity; CYP3A4: Cytochrome P450 3A4 (EC 1.14.13.97); Da

(g/mol) : Daltons (gram per mole); AUC_{0-t} and $AUC_{0-\infty}$: Area Under the Curve Relative and Infinity; Log P: Partition Coefficient; PVC/PE/PVdC: Tripac; MDDR: Drug Data Report; C_{max}: Peak Concentration of Drug in Blood; $t_{1/2}$: Half life; mRNA Messenger Ribonucleic Acid; SD: Standard Deviation; CrCl: Créatinine Clearance; Vss/F: Absorption-dependent Apparent Volume of Distribution at Steady State; EU: European Union; RT-PCR: Reverse Transcription-polymerase Chain Reaction; AE: Adverse Effect; ALT/AST: The Aspartate Aminotransferase-Alanine Aminotransferase; OATP: *Organic Anion-transporting Polypeptide; UTI: Urinary Tract Infection; SMA:* Spinal Muscular Atrophy.

REFERENCES

1. Hong IS, et al. Macitentan for the treatment of pulmonary arterial Hypertension. Ann Pharmacother (2014) 48: 538-547.
2. Raja SG. Macitentan, a tissue-targeting endothelin receptor antagonist for the potential oral treatment of pulmonary arterial hypertension and idiopathic pulmonary fibrosis. Curr Opin Investig Drugs (2010) 11:1066-1073.
3. Patel T and McKeage K. Macitentan: first global approval. Drugs (2014) 74: 127-133.
4. Iglarz M et al. Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. J Pharmacol Exp Ther (2008) 327:736-745.
5. Actelion receives US FDA approval of Opsumit (Macitentan, package insert) for the treatment of pulmonary arterial hypertension. Actelion; Summary of Product characteristics, Actelion Pharmaceuticals; Retrieved 22 October 2013.
6. USFDA, Medication Guide/lable, October 18, 2013.
7. Montani D, et al. Pulmonary arterial hypertension. Orphanet J Rare Dis (2013) 8:97.
8. Sitbon O and Morrell N Pathways in pulmonary arterial hypertension: the future is here. Eur Respir Rev (2012) 21:321-327.
9. Galie N, et al. Sustained effect of Macitentan, a novel oral endothelin receptor antagonist, on exercise capacity and the association of its measure with long-term outcomes in pulmonary arterial hypertension. Eur Heart J (2013).
10. Richard N, et al. Macitentan Reduces PAH-Related Hospitalizations: Results from the Randomized Controlled SERAPHIN Trial. American Thoracic Society, International Conference Abstracts. (2013) B98. Clinical trials in pulmonary hypertension.
11. Coghlan G, et al. Effect of Macitentan on pulmonary arterial hypertension-related hospitalizations: results from the randomized controlled SERAPHIN trial. Thorax (2013) 68: A143.
12. Rabinovistch M. Molecular pathogenesis of pulmonary arterial hypertension. J Clin Invest (2012)122: 4306-4313.
13. Wu Y, et al. An update on medical therapy for pulmonary arterial hypertension. Curr Hypertens Rep (2013) 15: 614-622.
14. Bolli MH, 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.
15. Clozel M (2011) Therapeutic compositions containing Macitentan. Patent US 20110136818 A1. Jun 9.
16. Sen S, et al. Renal, retinal and cardiac changes in type 2 diabetes are attenuated by macitentan, a dual endothelin receptor antagonist. Life Sci (2012) 91:658-668.
17. Kim SJ, et al. Antivascular therapy for multidrug-resistant ovarian tumors by macitentan, a dual endothelin receptor antagonist. Transl Oncol (2012) 5:39-47.
18. Corallo C, et al. Macitentan slows down the dermal fibrotic process in systemic sclerosis: in vitro findings. J Biol Regul Homeost Agents (2013) 27: 455-462.
19. Weiss J, et al. Interaction profile of Macitentan, a new non-selective endothelin-1 receptor antagonist, in vitro. Eur J Pharmacol (2013) 701: 168-175.
20. Asedi T. Macitentan for the treatment of pulmonary arterial hypertension, Journal Club Digest, Department of Pharmacy Practice, KU School of Pharmacy, University of Kansas, USA (2014).
21. Pulido T, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med (2013) 369: 809-818.
22. Dingemanse J 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) 13:391-405.
23. Http://www.drugs.com/cons/Macitentan.html //Truven Health Micromedex products.
24. Http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4979.

25. Http://www.opsumitrems.com/

26. Http://www.4-traders.com/ACTELION-LTD-442241/news/Actelion-Ltd--Macitentan-Opsumit-morbidity-and-mortality-data-in-pulmonary-arterial-hypertension-17253157/

27. Http://clinicaltrials.gov/show/NCT01743001

28. Gatfield J et al. Slow receptor dissociation kinetics differentiate Macitentan from other endothelin receptor antagonists in pulmonary arterial smooth muscle cells. PLoS ONE (2012) 7: e47662.

29. Http://www.medchemexpress.com/Macitentan.html

30. Kummer O, et al. Comparison of the dissolution and pharmacokinetic profiles of two galenical formulations of the endothelin receptor antagonist Macitentan. Eur J Pharm Sci (2009) 38: 384-388.

31. Bruderer S, et al. Absorption, distribution, metabolism, and excretion of Macitentan, a dual endothelin receptor antagonist, in humans. Xenobiotica (2012) 42: 901-910.

32. Sidharta PN, et al. Macitentan: entry-into-humans study with a new endothelin receptor antagonist. Eur J Clin Pharmacol (2011) 67: 977-984.

33. Sidharta PN, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of Macitentan, an endothelin receptor antagonist, in an ascending multiple-dose study in healthy subjects. J Clin Pharmacol (2013) 53:1131-1138.

34. Sidharta PN, et al. Pharmacokinetics of the novel dual endothelin receptor antagonist Macitentan in subjects with hepatic or renal impairment. J Clin Pharmacol (2013) 54: 291-300.

35. Http://reference.medscape.com/drug/opsumit-Macitentan-999880#0.

36. Http://medlibrary.org/lib/images-rx/opsumit/opsumit-02.jpg.

37. Sildenafil.In:ClinicalPharmacology.Tampa,FL:Elsevier/GoldStandard.http://www.clinicalpharmacology-ip.com/Forms/Monograph/monograph. Aspx? Cp.

38. Barst RJ, et al. Updated evidence-based treatment algorithms in pulmonary arterial hypertension. J Am Coll Cardiol (2009) 54: S78-84.