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R&D INSIGHT REPORT

Macitentan: First Global Approval

Trina Patel · Kate McKeage

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Abstract Macitentan (Opsumit®) is a novel dual endothelin receptor antagonist (ERA) with sustained receptor binding properties developed by Actelion Pharmaceuticals Ltd. In October 2013, oral macitentan 10 mg once daily received its first global approval in the US, followed closely by Canada, for the treatment of pulmonary arterial hypertension (PAH). The drug has also received a positive opinion in the EU from the Committee for Medicinal Products for Human Use for the treatment of PAH, and is under regulatory review in several other countries for the same indication. Endothelin (ET)-1 influences pathological changes via two ET receptor subtypes (ET_A and ET_B), to which it binds with high affinity. ET-1 is implicated in several forms of vascular disease making it a valid target for the treatment of pulmonary vascular diseases such as PAH. Clinical development is underway for other indications, including Eisenmenger syndrome, ischaemic digital ulcers secondary to systemic sclerosis, and glioblastoma. Macitentan was also evaluated in idiopathic pulmonary fibrosis; however, a phase 2 trial did not meet its primary endpoint and further investigation in this indication was discontinued. Macitentan was developed by modifying the structure of bosentan in the search for an optimal dual ERA with improved efficacy and tolerability compared with other ERAs. This article summarizes the milestones in the development of macitentan leading to this first approval for PAH.

This profile has been extracted and modified from the *Adis R&D Insight* drug pipeline database. *Adis R&D Insight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

T. Patel (✉)
Adis R&D Insight, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore, 0754 Auckland, New Zealand
e-mail: dru@adis.com

K. McKeage
Adis, Auckland, New Zealand

1 Introduction

Pulmonary arterial hypertension (PAH) is characterized by sustained elevation of pulmonary vascular resistance, leading to right ventricular failure and death [1]. Therapeutic agents used in the management of PAH include those that act on one of the mechanistic pathways (endothelin [ET], nitric oxide or prostacyclin) involved in the development of the disease, including endothelin-receptor antagonists (ERA; e.g. bosentan, ambrisentan), phosphodiesterase type 5 (PDE5) inhibitors (e.g. sildenafil, tadalafil) and prostacyclin analogues (e.g. epoprostenol, iloprost) [2].

ET-1 is upregulated in patients with PAH and influences pathological changes, including vasoconstriction, proliferation and fibrosis in the lung via two ET receptor subtypes, ET_A (located mainly in smooth muscle cells) and ET_B (located in endothelial and smooth muscle cells), to which it binds with high affinity [2]. The first ERA approved for use in patients with PAH was bosentan, which has been widely used since 2002, but has the potential to cause elevated levels of liver enzymes.

Macitentan (Opsumit®) is a new dual (ET_A and ET_B) ERA that was developed by modifying the structure of bosentan, with the aim of improving efficacy and safety compared with other ERAs [3]. Oral macitentan 10 mg once-daily was approved by the US FDA on 18th October 2013 [4], followed closely by Health Canada [5], for the treatment of PAH. As with other available ERAs, the label

Features and properties of macitentan

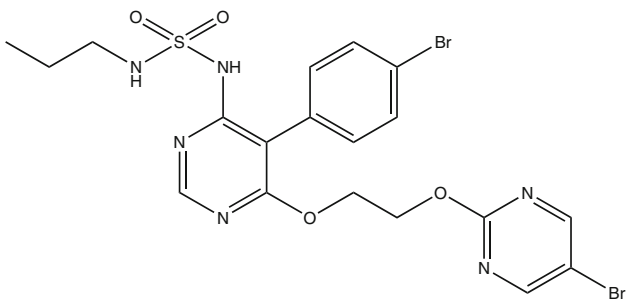
Alternative names	Opsumit®, Actelion-1; ACT-064992
Class	Bromobenzenes, Pyrimidines, Small-molecules, Sulfamides
Mechanism of action	Dual endothelin (ET) A and B receptor antagonist
Route of administration	Oral
Pharmacodynamics	Targets ET_A and ET_B receptors with a high tissue affinity and prevents ET-1 from binding to both receptors
Pharmacokinetics	Dose-proportional pharmacokinetics over dose range 1–30 mg/day
Treatment-emergent adverse events	
Most frequent (incidence >10 % and >3 % more frequent in 3 and 10 mg/day groups than placebo group)	Nasopharyngitis, headache, anaemia
Occasional	Reduced levels of haemoglobin
ATC codes	
WHO ATC code	C01 (Cardiac Therapy), C02 K-X (Other antihypertensives), D03 (Preparations for Treatment of Wounds and Ulcers), L01X (Other Antineoplastic Agents), R07A-X (Other respiratory system products)
EphMRA ATC code	C1 (Cardiac Therapy), C2 (Antihypertensives), D3A (Wound Healing Agents), L1X (All Other Antineoplastics), R7X (All Other Respiratory System Products)
Chemical name	*N*-[5-(4-bromophenyl)-6-{2- [(5-bromopyrimidin-2-yl)oxy] ethoxy}pyrimidin-4-yl] -*N*′-propylsulfamide

carries a Boxed Warning stating that the drug should not be used in pregnant women due to harmful effects on the developing foetus [6]. As with other drugs in this class, female patients will only be able to receive the drug through the Opsumit Risk Evaluation and Mitigation Strategy (REMS) programme [6]. Also in October 2013, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a positive opinion regarding the approval of oral macitentan 10 mg as monotherapy or in combination for the long-term treatment of adults with PAH of WHO Functional Class II to III [7]. Approvals from the FDA and Health Canada and the CHMP's positive opinion were primarily based on data from the phase III SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Hypertension to improve clINical outcome) study [8]. Macitentan has also been submitted for regulatory review for use in PAH in several other countries [9].

Macitentan is also in development for use in Eisenmenger syndrome [10], ischaemic digital ulcers secondary to systemic scleroderma (systemic sclerosis) [11] and glioblastoma [12]. The clinical trial programme investigating the use of macitentan in the treatment of idiopathic pulmonary fibrosis was terminated because the primary endpoint (change in forced vital capacity) was not met in the MUSIC (Macitentan Use in an Idiopathic Pulmonary Fibrosis Clinical) trial [13]. The efficacy and tolerability of macitentan were established in a phase 2 trial in patients with essential hypertension, in which macitentan had a greater effect on blood pressure reduction than placebo or enalapril [14].

1.1 Company Agreements

Actelion Pharmaceuticals Ltd discovered macitentan in 2002, and licensed the compound to Nippon Shinyaku in Japan for the treatment of PAH in February 2010 [15]. Under the terms of the agreement, both companies agreed to jointly conduct clinical trials in Japan [15]. Actelion Pharmaceuticals Ltd has been granted patents relating to the composition of matter of macitentan worldwide.



Chemical structure of macitentan

2 Scientific Summary

2.1 Pharmacodynamics

2.1.1 In Vitro Studies

Macitentan targets ET_A and ET_B receptors with a high tissue affinity and prevents ET-1 from binding to both receptors [16]. Macitentan has strong affinity for lipids, with a distribution of 800 to 1 between octanol and aqueous buffer. The overall affinity of macitentan for the lipid milieu was 40- and 2000-fold greater than that of bosentan and ambrisentan, respectively [16]. In preclinical models, macitentan exhibited sustained receptor occupancy compared with other ERA's (bosentan and ambrisentan) [17].

Macitentan demonstrates a greater inhibitory effect at ET_A than ET_B receptors [16]. In microsomal membranes of Chinese hamster ovary cells, macitentan and its major active metabolite (ACT-132577) inhibited binding of ^{125}I-ET-1 to recombinant ET_A receptors, with mean concentrations that produce 50 % inhibition (IC_{50}) of 0.5 and 3.4 nM, respectively [16]. Mean IC_{50} values for macitentan and ACT-132577 for ET_B receptors were 391 and 987 nM, respectively. In functional assays, macitentan and ACT-132577 fully inhibited intracellular calcium increase induced by ET-1 in primary human smooth muscle cells, rat aortic smooth muscle cells and mouse fibroblast cells [16]. The IC_{50} of ACT-132577 was approximately 10-fold higher than that of the parent compound.

Macitentan and ACT-132577 inhibited ET-1-induced contractions in isolated rat aorta (mediated by ET_A receptors) and sarafotoxin S6c-induced contractions in isolated rat trachea (mediated by ET_B receptors) [16]. The ET_A/ET_B receptor inhibitory potency ratio for macitentan and ACT-132577 was 50 1 and 16 1, respectively [16].

The selectivity of macitentan for ET_A and ET_B receptors was demonstrated in a panel of radioligand binding assays, in which macitentan (10 μM) did not inhibit the activity of any of the ligands by >50 % [16].

ET-1 is thought to be a key mediator of fibroblast activation and proliferation, leading to vascular damage in patients with scleroderma [18]. In dermal fibroblasts taken from lesional skin from sclerodermic patients, macitentan and ACT-132577 reduced levels of alpha smooth muscle actin (αSMA) after 48 h compared with αSMA levels in basal conditions ($p < 0.01$) [18].

2.1.2 In Vivo Studies

Macitentan increased plasma ET-1 levels in normotensive rats, thereby demonstrating blockade of ET_A and ET_B receptors [16]. The pharmacological potency of macitentan is greater than that of bosentan in vivo, as the increase in ET-1 plasma levels was achieved at a macitentan dose that was 10-fold lower [16].

Mean arterial blood pressure (BP) is reduced dose dependently with macitentan and bosentan, but neither drug has any effect on heart rate [16]. The mean effective doses of macitentan and bosentan that reduced mean arterial BP in 50 % (ED_{50}) of hypertensive deoxycorticosterone acetate salt rats were 1 and 10 mg/kg, respectively [16]. The decrease in BP was maintained for approximately 40 h with the maximum dose of macitentan (10 mg/kg) and for 20 h with the maximum dose of bosentan (100 mg/kg).

Oral macitentan and bosentan for 4 weeks dose-dependently prevented the development of pulmonary hypertension and right ventricular hypertrophy in the monocrotaline rat model of pulmonary hypertension [16]. The dosages at which maximum efficacy was achieved with regard to the prevention of right ventricular hypertrophy were macitentan 30 mg/kg/day and bosentan 300 mg/kg/day. Macitentan 30 mg/kg/day significantly ($p < 0.002$) improved 42-day survival of monocrotaline rats, with a 66 % reduction in mortality compared with vehicle-treated rats [16]. Overall, in a rat model of bleomycin-induced pulmonary fibrosis, 19 days treatment with macitentan 100 mg/kg/day was more effective than bosentan 300 mg/kg/day in preventing the development of lung fibrosis and right ventricular hypertrophy, which is thought to reflect the greater ability of macitentan to distribute into the tissues [19]

Macitentan (30 mg/kg orally for 24 weeks) partially prevented the development of renal vasoconstriction ($p < 0.001$), increased renal blood flow ($p < 0.001$) and improved the glomerular filtration rate ($p < 0.05$) in streptozotocin-induced diabetic rats compared with untreated controls [16]. Vascular and tubulointerstitial lesions were reduced with chronic macitentan treatment, and proteinuria was partially prevented. In addition, macitentan prevented the increase in vascular endothelial growth factor (VEGF) expression in the retina observed in diabetic rats [16]. In diabetic mice, treatment with macitentan (25 mg/kg/day) attenuated chronic complications affecting multiple organs in type 2 diabetes, including renal, retinal and cardiac changes, thereby demonstrating the role of ET-1 activation in the pathogenesis of diabetic complications [20].

Treatment with macitentan enhanced paclitaxel-induced cytotoxicity in nude mice following injection of human ovarian cancer cells (SKOV3ip1 and IGROV1) into the peritoneal cavity [21]. Paclitaxel plus macitentan signifi-

cantly decreased tumour incidence, tumour weight and the incidence of ascites compared with paclitaxel alone ($p < 0.05$ for all) [21]. Macitentan and macitentan plus paclitaxel were associated with reduced phosphorylation of ET receptors and suppressed survival pathways of tumour cells [21]. Furthermore, in the same mouse model, multidrug-resistant ovarian cancer cells that express the endothelin axis were sensitive to macitentan, and following macitentan treatment were resensitized to paclitaxel and cisplatin [22].

2.1.3 In Healthy Subjects

Single doses of macitentan ranging from 0.2 to 600 mg led to dose-dependent increases in ET-1 concentrations, and increases were significantly greater than those with placebo at doses ≥25 mg in a double-blind study in healthy subjects [23]. Furthermore, at steady-state in an ascending-dose study, plasma ET-1 concentrations showed a dose dependent increase with maximum effects achieved at macitentan 10 mg/day, indicating full receptor blockade at this level [24]. Macitentan had no consistent effect on total bile salts [23, 24].

In a thorough corrected QT (QTc) study in healthy subjects, there was no evidence of prolonged cardiac repolarization or other ECG changes [25].

2.2 Pharmacokinetics

The pharmacokinetics of once daily oral macitentan (1–30 mg) are dose proportional and characterized by slow absorption as a result of low aqueous solubility [6, 23].

After oral administration, the maximum plasma concentration (C_{max}) of macitentan is reached in about 8 hours [6]. The absolute bioavailability of the drug is unknown [6]. Following administration of macitentan 10 mg/day for 10 days in healthy subjects, mean C_{max} and area under the plasma concentration-time curve (AUC) values for macitentan were 371 ng/mL and 5,400 ng·h/mL, respectively [24]. Corresponding values for the active metabolite ACT-132577 were 802 ng/mL and 15,541 ng·h/mL [24]. After multiple daily doses in healthy male volunteers, steady-state conditions were reached on day 3 for macitentan and day 7 for ACT-132577 [24].

Macitentan and ACT-132577 are highly bound to plasma proteins (>99 %) [6]. The apparent volume of distribution in healthy subjects was 50 L for macitentan and 40 L for ACT-132577. Exposure to macitentan and its active metabolite is not affected by food.

Macitentan does not accumulate to any great extent, with an accumulation of approximately 1.5 across the dose range of 1 to 30 mg/day [24]. In contrast, ACT-132577 accumulates to a clinically significant extent, with ratios between 7.1 and 9.9 for the dose range of 1 to 30 mg/day.

The apparent elimination half-lives of macitentan and ACT-132577 following oral administration are approximately 16 and 48 hours, respectively [6].

Macitentan is primarily metabolized by oxidative depropylation by cytochrome P450 (CYP), mainly CYP3A4 and to a lesser extent CYP2C19, to form ACT-132577 [6]. At steady state in patients with PAH, the exposure to ACT-132577 is about 3-fold higher than that of macitentan and is expected to contribute about 40 % of the total pharmacological activity. After administration of radiolabeled macitentan to healthy subjects, approximately 50 % of drug material was eliminated in urine, but none in the form of unchanged drug or ACT-132577, and approximately 24 % was eliminated in faeces [26].

There were minor differences in the pharmacokinetics of macitentan between healthy Caucasian and Japanese subjects and between male and female subjects, but none were considered to be clinically relevant and dose adjustments based on Japanese ethnicity or sex are not considered necessary [27]. Similarly, there were no clinically relevant effects on the pharmacokinetics of macitentan in subjects with severe renal impairment or mild, moderate or severe hepatic impairment [28].

2.2.1 Drug Interactions

Bosentan is known to be associated with certain drug-drug interactions [29]. Macitentan has a similar or higher potency for induction and inhibition of drug metabolizing enzymes and transporters to that of bosentan, but as it is associated with relatively low plasma concentrations and minimal accumulation in the liver [29].

When macitentan was coadministered with ketoconazole (a strong CYP3A4 inhibitor) in healthy subjects, the macitentan AUC was increased approximately 2-fold and the ACT-132577 AUC was reduced by approximately 26 % [30]. The concomitant use of macitentan with strong CYP3A4 inhibitors should be avoided [6].

Concomitant treatment with macitentan and ciclosporin (a CYP3A4 inhibitor) did not have a clinically relevant effect on exposure to macitentan or its metabolites at steady state [31]. However, concomitant treatment with macitentan and rifampicin (a strong inducer of CYP3A4) significantly reduced exposure to macitentan at steady state, but did not affect exposure to ACT-132577 to a clinically relevant extent [31]. The concomitant use of macitentan with strong CYP3A4 inducers should be avoided [6].

2.3 Therapeutic Trials

The efficacy and tolerability of macitentan 3 or 10 mg/day in the treatment of PAH in patients aged ≥12 years (n = 742) was evaluated in the randomized, double-blind, placebo-controlled, multicenter, event-driven phase 3 SERAPHIN study [8]. The primary endpoint was a composite of the time to the first occurrence of death, atrial septostomy, lung transplantation, initiation of treatment with intravenous or subcutaneous prostanoids, or worsening of pulmonary arterial hypertension. Clinical assessments (such as 6 min walk distance test and change in WHO functional class) were performed at randomization or screening and at months 3 and 6, and at subsequent 6 monthly intervals up to the end of treatment. The mean duration of treatment in the macitentan 3 and 10 mg/day and placebo groups was 99.5, 103.9 and 85.3 weeks, respectively.

Both dosages of macitentan significantly reduced the risk of morbidity or mortality events versus placebo [8]. A primary endpoint event occurred in 38.0 % of patients in the macitentan 3 mg/day group, 31.4 % in the macitentan 10 mg/day group and 46.4 % in the placebo group. Hazard ratios in the respective macitentan groups versus placebo were 0.70 (97.5 % CI, 0.52 to 0.96; p = 0.01) and 0.55 (97.5 % CI, 0.39 to 0.76; p < 0.001) [8]. The most frequent event among primary endpoint criteria was worsening of PAH. The efficacy of macitentan was observed regardless of whether PAH therapies were being administered at baseline.

Hazard ratios for the secondary composite endpoint of death or hospitalization due to PAH in the macitentan 3 or 10 mg/day groups versus placebo were 0.67 (97.5 % CI, 0.46 to 0.97; p = 0.01) and 0.50 (97.5 % CI, 0.34 to 0.75; p < 0.001) [8].

The 6 min walk distance increased by a mean of 7.4 (p = 0.01) and 12.5 m (p = 0.008) in the macitentan 3 and 10 mg/day groups, respectively, compared with a mean decrease of 9.4 m in the placebo group after 6 months of treatment [8]. The WHO functional class improved from baseline to month 6 in 20 % (p = 0.04), 22 % (p = 0.006) and 13 % of patients in each of the groups, respectively.

In a subgroup of patients ($n = 145$) participating in a haemodynamic study, pulmonary vascular resistance significantly decreased and the cardiac index significantly increased in both macitentan groups compared with the placebo group [8].

Key clinical trials of macitentan by Actelion Pharmaceuticals Ltd

Active treatment	Indication	Phase	Status	Location	Identifiers
Macitentan	PAH	3	Complete	Multinational	NCT00660179 (AC-055-302/SERAPHIN)
Macitentan	PAH	3	On-going, enrolment complete	Multinational	NCT00667823 (AC 055 303/SERAPHIN OL)
Macitentan	PAH	3	Recruiting	USA	NCT01841762 (AC-055-401/SYMPHONY)
Macitentan	PAH	3	Recruiting	USA	NCT01847014 (AC-055-402/SYMPHONYext)
Macitentan	Eisenmenger syndrome	3	Recruiting	Multinational	NCT01743001/EudraCT 2012-003335-33 (AC-055-305/MAESTRO)
	Eisenmenger syndrome	3	Recruiting	Multinational	NCT01739400/EudraCT 2012-004411-31 (AC-055-308/MAESTRO-OL)
Macitentan	Ischaemic digital ulcers secondary to systemic scleroderma	3	On-going, enrolment complete	Multinational	NCT01474109 (AC-055C301/DUAL-1)
Macitentan	Ischaemic digital ulcers secondary to systemic scleroderma	3	Recruiting	Multinational	NCT01474122 (AC-055C302/DUAL-2)
Macitentan plus temozolomide	Glioblastoma	1	Recruiting	USA	NCT01499251 (AC-055-115)
Macitentan	IPF	2	Complete	Multinational	NCT00903331 (MUSIC/AC-055B201)
Macitentan	IPF	2	Withdrawn prior to enrolment	Multinational	NCT01346930 (MUSIC OL/NCT01346930)

IPF idiopathic pulmonary fibrosis, *PAH* pulmonary arterial hypertension

2.4 Adverse Events

Macitentan was generally well tolerated in the SERAPHIN trial [8]. A similar proportion of patients in the macitentan 3 and 10 mg/day and placebo groups discontinued therapy due to an adverse event (13.6, 10.7 and 12.4 %, respectively), and experienced at least one serious adverse event (52.0, 45.0 and 55.0 %, respectively).

The most frequently reported adverse events (occurring in >12 % of macitentan recipients) were worsening of PAH (30 % of patients in the macitentan 3 mg/day group, 22 % in the macitentan 10 mg/day group and 35 % in the placebo group), upper respiratory tract infection (20, 15 and 13 %), peripheral oedema (16, 18 and 18 %), nasopharyngitis (15, 14 and 10 %), right ventricular failure (15, 13 and 23 %), headache (13, 14 and 9 %) and anaemia (9, 13 and 3 %) [8]. Only nasopharyngitis, headache and anaemia occurred in a significantly higher proportion of patients in the macitentan groups than in the placebo group.

With regard to laboratory abnormalities, the proportion of patients in the macitentan 3 and 10 mg/day and placebo groups with AST or ALT levels >3 times the upper limit of normal was generally similar across the three treatment groups (3.6, 3.4 and 4.5 %, respectively), as were the proportions with AST or ALT levels >3 times the ULN and bilirubin levels >2 times the ULN (2.1, 1.7 and 1.7 %, respectively) [8]. A decrease in haemoglobin levels to ≤8 g/dL occurred in 1.7, 4.3 and 0.4 % of patients in each group, respectively.

2.5 Ongoing Clinical Trials

The long-term efficacy and tolerability of macitentan 10 mg once daily in patients with PAH are being evaluated in a single-arm, extension of the SERAPHIN study (SERAPHIN OL) (NCT00667823).

In April 2013, Actelion initiated enrolment in the SYMPHONY study, a phase 3 psychometric validation trial of the new PAH-SYMPACT™ instrument, a quality of life questionnaire for patients with PAH (NCT01841762). Patients are receiving macitentan 10 mg once daily for 4 months. An extension to the SYMPHONY trial (SYMPHONYext) was initiated in September 2013, and will assess the long-term safety of macitentan in patients with PAH (NCT01847014).

In patients with Eisenmenger Syndrome, the double-blind, phase 3, 16-week MAESTRO (Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity) study (NCT01743001), and an open-label extension (NCT01739400) are evaluating the efficacy and tolerability of macitentan 10 mg once daily.

Two phase 3 trials (DUAL 1 and DUAL 2) are evaluating macitentan 3 and 10 mg once daily in the treatment of digital ulcers in systemic sclerosis patients (NCT01474109, NCT01474122).

Macitentan is also being evaluated in a phase 1, dose escalation study in patients with recurrent glioblastoma (NCT01499251).

3 Current Status

Oral macitentan (10 mg once daily) received its first global approval in the US on the 18th of October 2013. In the US, macitentan is indicated for the treatment of PAH (WHO Group I) to delay disease progression and it was shown to reduce hospitalizations for PAH. The drug was also recently approved in Canada and received a positive CHMP opinion in the EU for use at the same dosage for the long-term treatment of adults with PAH of WHO Functional Class II to III.

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