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Newcastle University

Health Technology Briefing
May 2022

Macitentan-tadalafil for treating pulmonary arterial hypertension

Company/Developer	Janssen-Cilag Ltd.

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29749	NICE ID: 10517	UKPS ID: 652225

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Macitentan and tadalafil as a fixed-dose combination (FDC) is in clinical development for the treatment of pulmonary arterial hypertension (PAH). PAH is a rare disorder in which there is severe narrowing of the arteries of the lungs. More pressure is needed to force blood through the narrowed artery which this leads to high blood pressure in the lungs. Common symptoms of PAH are shortness of breath, fainting or feeling faint, dizziness, chest pain and a rapid heart rate. There is currently no cure for PAH, and more effective treatments are needed.

Macitentan, works by blocking endothelin receptors. These are part of a natural mechanism in the body that can cause arteries to narrow. By blocking these receptors, macitentan helps widen the arteries in the lungs thereby reducing blood pressure. Tadalafil belongs to a group of medicines called 'phosphodiesterase type 5 (PDE5) inhibitors', which block the PDE5 enzyme. When the enzyme is blocked, a substance called 'cyclic guanosine monophosphate' (cGMP) cannot be broken down and remains in the blood vessels. In patients with PAH, this lowers the blood pressure in the lungs and improves symptoms. Administering a combination of macitentan and tadalafil has been found to be safe and effective in decreasing mean pulmonary arterial pressure. If licenced, a FDC of macitentan and tadalafil would offer PAH patients the advantages provided by the combination of macitentan and a PDE-5 inhibitor in a single, once daily dose tablet. This could facilitate compliance and reduce the risk of medication errors.

Proposed Indication

Subjects with pulmonary arterial hypertension (PAH).[1]

Technology

Description

Macitentan is an orally active potent endothelin receptor antagonist which binds to the endothelin A and B receptors (ET_A and ET_B). Macitentan displays high affinity and sustained occupancy of the ET receptors in human pulmonary arterial smooth muscle cells. This prevents endothelin-mediated activation of second messenger systems that result in vasoconstriction and smooth muscle cell proliferation.[2]

Tadalafil is a selective, reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5). Pulmonary arterial hypertension (PAH) is associated with impaired release of nitric oxide by the vascular endothelium and consequent reduction of cGMP concentrations within the pulmonary vascular smooth muscle. PDE5 is the predominant phosphodiesterase in the pulmonary vasculature. Inhibition of PDE5 by tadalafil increases the concentrations of cGMP resulting in relaxation of the pulmonary vascular smooth muscle cell and vasodilation of the pulmonary vascular bed.[3]

Macitentan and tadalafil FDC is currently in clinical development for the treatment of PAH. In the phase III clinical trial (NCT03904693), patients will be given a film-coated tablet with a combination of 10 mg macitentan and 40 mg tadalafil, to be administered orally once daily.[1]

Key Innovation

A combination of macitentan and tadalafil has been found to have a synergistic effect versus either single agent in decreasing mean pulmonary arterial pressure without increasing the risk of exaggerated systemic vasodilation.[4] Studies investigating the efficacy of administering macitentan in combination with a PDE5 inhibitor contributed to updated European Society of Cardiology and European Respiratory Society guidelines, which recommend that combination therapy be given as sequential or up-front combination therapy if treatment targets are not met.[4,5]

If licenced, a FDC of macitentan and tadalafil would offer PAH patients the advantages provided by the concomitant use of macitentan and a PDE-5 inhibitor in a single, once daily dose tablet. This could facilitate compliance and reduce the risk of medication errors.[4]

Regulatory & Development Status

Macitentan has a Marketing Authorisation in the UK as a monotherapy or in combination for the long-term treatment of PAH in adults of WHO Functional Class II to III.[2]

Tadalafil has a Marketing Authorisation in the UK for the treatment of erectile dysfunction in males and for the treatment of WHO Functional Class II and III PAH.[3]

Macitentan and tadalafil FDC does not currently have a Marketing Authorisation in the UK.
Macitentan and tadalafil FDC is not currently in phase II or III trials for any other indication.

Patient Group

Disease Area and Clinical Need

PAH is a rare, progressive disorder characterised by high blood pressure (hypertension) in the arteries of the lungs (pulmonary arteries).[6] PAH occurs when most of the very small arteries throughout the lungs narrow in diameter, which increases the resistance to blood flow through the lungs. To overcome the resistance, blood pressure increases in the pulmonary artery and in the right ventricle of the heart, which is the chamber that pumps blood into the pulmonary artery. This increase in blood pressure can result in damage to the right ventricle of the heart.[7] The World Health Organisation (WHO) functional class system defines the severity of an individual's symptoms and how they impact on day-to-day activities. WHO functional class II have pulmonary hypertension resulting in slight limitation of physical activity and experience PAH symptoms when carrying out ordinary physical activity. WHO functional class III results in marked limitation of physical activity, which can cause difficulty in carrying out general day-to-day activities, such as household chores.[8] PAH can be divided into subtypes depending on the cause of disease. Idiopathic PAH is where the exact cause is unknown. Familial PAH occurs when there is a particular genetic mutation present that can cause PAH. PAH can also be associated with other conditions including connective tissue diseases, congenital heart problems, pulmonary veno-occlusive disease and HIV.[9,10] Common symptoms of PAH are shortness of breath, fainting or feeling faint, dizziness, chest pain and a rapid heart rate.[7] There is currently no cure for PAH.[11]

Pulmonary hypertension affects approximately one in 20,000 people in the UK.[12] The estimated annual incidence of diagnosed PAH in the general population ranges from 0.9 to 7.6 cases per million persons, while the prevalence of diagnosed PAH in the general population is between 6.6 and 26 cases per million persons.[11] In England (2020/21), there were 1,504 finished consultant episodes (FCEs) and 1,129 admissions for primary pulmonary hypertension (ICD-10 code I27.0), which resulted in 724 day cases and 3,155 FCE bed days.[13] As of 2012, PAH survival at 1, 3, and 5 years was 68, 48, and 34% respectively.[14]

Recommended Treatment Options

Three groups of specific drugs are used to treat PAH: prostanoids, endothelin receptor antagonists, and PDE5 inhibitors. Although in severe cases an upfront combination therapy may be considered, generally a monotherapy is initiated first and eventually expanded to a sequential combination of drugs.[14] The following therapies are currently recommended by the NHS for the treatment of PAH:[11,15]

- Macitentan
- Bosentan
- Ambrisentan
- Tadalafil
- Sildenafil
- Epoprostenol
- Iloprost
- Selexipag

Monotherapy with an oral PDE5 inhibitor (sildenafil or tadalafil) will be routinely commissioned as first line therapy. Where a PDE5 inhibitor is not clinically appropriate, an endothelin receptor antagonist (bosentan, ambrisentan or macitentan) may be substituted. Patients who have initially responded to first-line therapy but then deteriorated may be considered for dual therapy with combinations involving a PDE5 inhibitor.[11]

Clinical Trial Information

Trial	NCT03904693, 2014-004786-25; Prospective, Multi-centre, Double-blind, Randomized, Active-controlled, Triple-dummy, Parallel-group, Group-sequential,

	Adaptive Phase 3 Clinical Study to Compare the Efficacy and Safety of Macitentan and Tadalafil Monotherapies With the Corresponding Fixed Dose Combination in Subjects With Pulmonary Arterial Hypertension (PAH), Followed by an Open-label Treatment Period With Macitentan and Tadalafil Fixed Dose Combination Therapy **Phase III** – Recruiting **Locations:** 7 EU countries, USA, Canada and other countries. **Primary completion date:** April 2022
Trial Design	Randomised, parallel assignment, quadruple-blind
Population	N=170 (planned); aged 18 years and older; subjects with confirmed diagnosis of symptomatic PAH belonging to one of the following subgroups: idiopathic, heritable, drug- or toxin-induced, associated with connective tissue disease, HIV infection, portal hypertension or congenital heart disease with simple systemic-to-pulmonary shunt with persistent pulmonary hypertension documented by a right heart catheterization ≥ 1 year after surgical repair
Intervention(s)	FDC macitentan/tadalafil film coated oral tablet with 10mg macitentan and 40mg tadalafil + placebo macitentan + placebo tadalafil
Comparator(s)	Monotherapy macitentan 10mg film coated oral tablet + placebo tadalafil + placebo FDC or monotherapy tadalafil 40mg film coated tablets (2 x 20mg tablets) + placebo macitentan + placebo tadalafil
Outcome(s)	Primary outcome: Change in pulmonary vascular resistance (PVR) expressed as the ratio of geometric means of end of double-blind treatment (EDBT) to baseline [Time frame: from baseline to EDBT (week 16)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of macitentan plus tadalafil FDC is not yet known.

Macitentan is already marketed in the UK; a pack of 30 x 10mg tablets costs £2,306.[16]

Tadalafil is already marketed in the UK; a pack of 8 x 20mg tablets costs between £2.54 and £109.98.[17]

Relevant Guidance

NICE Guidance

- NICE interventional procedures guidance. Balloon pulmonary angioplasty for chronic thromboembolic pulmonary hypertension (IPG554). April 2016.

NHS England (Policy/Commissioning) Guidance
• NHS England. Clinical Commissioning Policy: Selexipag for Treating Pulmonary Arterial Hypertension (Adults). 170104P. December 2018. • NHS England. Clinical Commissioning Policy: Riociguat for Pulmonary Arterial Hypertension. 16055/P. February 2017. • NHS England. Clinical Commissioning Policy: National Policy for Targeted Therapies for the Treatment of Pulmonary Hypertension in Adults. NHS England/A11/P/b. May 2014.
Other Guidance
• European Society of Cardiology. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. 2015.[5] • MJ Connolly and G Kovacs. Pulmonary hypertension: a guide for GPs. 2012.[14]

Additional Information

References

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.