Health Technology Briefing
October 2022

Macitentan for treating pulmonary arterial hypertension in children

Company/Developer	Janssen

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 12311	NICE ID: 11805	UKPS ID: 666820

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Macitentan is in clinical development for the treatment of pulmonary arterial hypertension (PAH) in children. 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 that 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 few NICE recommended treatments available for paediatric patients with PAH. There is an unmet need for effective treatments options for these patients.

Macitentan is administered orally and works by blocking endothelin receptors (a type of protein). These are part of a natural mechanism in the body that can cause arteries to narrow. In patients with PAH, this mechanism is overactive and, by blocking these receptors, macitentan helps to widen the arteries in the lungs thereby reducing the blood pressure. If licensed, macitentan would provide an additional treatment option for PAH in children.

Proposed Indication

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

Technology

Description

Macitentan (Opsumit, ACT-064992) is an orally active potent endothelin receptor antagonist, which binds to the endothelin A and B receptors (ETA and ETB). Endothelin (ET)-1 and its receptors (ETA and ETB) mediate a variety of effects such as vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation. In disease conditions such as PAH, the local ET system is upregulated and is involved in vascular hypertrophy and in organ damage. 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]

In the phase III clinical trial (TOMORROW, NCT02932410) patients will be administered macitentan orally once daily at a dose adjusted to the participant's age (for those < 2 years old) or the participant's weight (for those ≥ 2 years old).[1]

Key Innovation

In a paediatric population, macitentan was shown to be associated with improvements in invasive haemodynamics, echocardiographic variables of right ventricular systolic function and serum N-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations. Macitentan is given once-a-day. Compared with other endothelin receptor antagonists that can be used to treat PAH in adults, macitentan has lower risks of both drug-drug interactions and adverse effects, however the efficacy and safety of macitentan in children has not been established.[3-5] The management of children remains challenging because treatments have long depended on evidence-based adult studies and the clinical experience of paediatric experts.[6] There remains an unmet need for PAH treatments that are proven to be effective in treating paediatric PAH.

If licensed, macitentan will provide an additional treatment for PAH in children.

Regulatory & Development Status

Macitentan has Marketing Authorisation in the UK for the long-term treatment of PAH in adult patients of WHO FC II to III.[2]

Macitentan is also in phase II/III clinical development for chronic thromboembolic pulmonary hypertension.[7]

Macitentan has been awarded an orphan drug designation by the EMA in September 2011 for the treatment of PAH.[8]

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).[9] 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.[10] 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 I patients are without any resulting limitation in physical activity. WHO functional class II patients 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.[11] PAH can be associated with an existing condition, such as congenital heart disease. Sometimes there is no known cause, this is called idiopathic pulmonary arterial hypertension.[12] Common symptoms of PAH are shortness of breath, fainting or feeling faint, dizziness, chest pain and a rapid heart rate.[10] There is currently no cure for PAH.[13]

In the UK (2010), the estimated incidence of childhood idiopathic PAH was 0.48 per million children per year. The prevalence of childhood idiopathic PAH was 2.07 cases per million children.[14] The children's specialist PH centre (Great Ormond Street Hospital) is expected to manage 100 patients per annum with PAH or chronic thromboembolic pulmonary hypertension (CTEPH).[15]

Recommended Treatment Options

Treatments to help manage symptoms in children with PAH may include:[16]

- Medication to relax the blood vessels in the lungs, to encourage new blood vessels to grow or to stop blood clots from forming
- Water tablets (diuretics)
- Oxygen therapy
- Surgery

Various other medications can be used to help children with PAH, including anticoagulants, digoxin, calcium-channel blockers and vasodilators.[17] The following targeted PAH therapies are licenced for use in children:[18,19]

- Bosentan
- Sildenafil

The use of ambrisentan is not currently licenced in the UK, however it is sometimes used off label for the treatment of paediatric PAH.[20]

Clinical Trial Information

Trial	**TOMORROW**, NCT02932410, 2016-001062-28; A Multicenter, Open-label, Randomized, Study With Single-arm Extension Period to Assess the Pharmacokinetics, Safety and Efficacy of Macitentan Versus Standard of Care in Children With Pulmonary Arterial Hypertension **Phase III** – Recruiting **Location(s):** 7 EU countries, USA, Canada and other countries **Primary completion date:** February 2024
Trial Design	Randomised, parallel assignment, open label
Population	N=300 (planned); PAH diagnosis confirmed by historical RHC; PAH belonging to the NICE 2013 Updated Classification Group 1; aged 1 month to 17 years

Intervention(s)	Macitentan (oral)
Comparator(s)	Standard of care as per site's clinical practice
Outcome(s)	Primary outcome measures: • Participants greater than or equal to (>=) 2 years: observed steady-state trough plasma concentration of macitentan and its active metabolite ACT-132577 at week 12 [time frame: week 12] • Participants less than (<) 2 years: observed steady state trough plasma concentration of macitentan and its active metabolite ACT-132577 at week 4 [time frame: week 4] See trial record for full list of other outcome measures.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Macitentan is already marketed in the UK; a pack of 30 x 10mg tablets costs £2,306.[21]

Relevant Guidance

NICE Guidance

- NICE interventional procedures guidance. Telemetric adjustable pulmonary artery banding for pulmonary hypertension in infants with congenital heart defects (IPG505). November 2014.

NHS England (Policy/Commissioning) Guidance

No relevant guidance identified.

Other Guidance

- European Respiratory Society. Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. 2018.[6]
- The European Paediatric Pulmonary Vascular Disease Network. Treatment of children with pulmonary hypertension. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. 2016.[22]

Additional Information

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