

**EVIDENCE BRIEFING  
OCTOBER 2018**

**Udenafil for congenital heart disease in  
adolescents after fontan palliation**

<b>NIHRI ID</b>	11585	<b>NICE ID</b>	9884
<b>Developer/Company</b>	Mezzion Pharma Co. Ltd	<b>UKPS ID</b>	N/A

<b>Licensing and market availability plans</b>	Currently in phase III clinical trials.
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**SUMMARY**

Udenafil as an oral tablet is in clinical development for congenital heart disease in adolescents after Fontan palliation. Functional single ventricle congenital heart disease is a condition in which babies are born with one of their lower heart chambers (ventricles) not working. As a result, the heart cannot pump blood properly to the lungs and the rest of the body. The Fontan operation is the final of three surgeries in the strategy of staged palliation for children born with congenital heart defects resulting in functional single-ventricle physiology. Fontan patients may have a shortened life span, often not surviving past the third or fourth decade of life, due to many factors including deteriorating ventricular performance and increasing pulmonary vascular resistance.

Udenafil works by blocking the enzyme phosphodiesterase type 5 which regulates the breakdown of 'cyclic guanine monophosphate' (cGMP) in the blood vessels of the lungs. Increased levels of cGMP leads to dilation (widening) of the vessels improving blood flow to the lungs, reducing the burden on the heart and improving oxygen supply to the blood. This is expected to improve the symptoms of the condition and may offer an additional treatment option for adolescents (12-18 years old) for the management of congenital heart disease after Fontan palliation who currently have few effective therapies available.

## PROPOSED INDICATION

Congenital heart disease in adolescents (12-18 years old) after Fontan palliation<sup>1</sup>

## TECHNOLOGY

### DESCRIPTION

Udenafil (DA8159) is a novel phosphodiesterase 5 (PDE5) inhibitor.<sup>1</sup> PDE5 selectively hydrolyses cyclic guanosine monophosphate (cGMP). The biological activity and levels of cGMP are regulated by the rate of its breakdown by phosphodiesterases. The inhibition of phosphodiesterase isoenzymes allows modulation of associated G-protein and calcium signaling functions.<sup>2</sup>

PDE5 is expressed in arteries of many organs in the body including the coronary arteries. Three isoforms of PDE5 have been described: PDE5A1, PDE5A2, and PDE5A3. Although the A1 and A2 isoforms are expressed in several tissues, A3 is confined to smooth muscle and cardiac tissue. cGMP concentration rises and PDE5 expression is upregulated in a variety of cardiac disorders. The downstream effects of cGMP and PDE5 can be modified by PDE5 inhibition in the presence of enhanced sympathetic stimulation. PDE5 inhibitors have been used clinically to treat erectile dysfunction and pulmonary hypertension.<sup>2</sup>

In the phase III clinical trial (FUEL; NCT02741115), udenafil is administered by one oral tablet twice daily for 26 weeks.<sup>3</sup> In the phase III extension study (FUELExten; NCT03013751), udenafil will be administered for 52 weeks.<sup>4</sup> Dosing specifics are not reported on the trial registries.

### INNOVATION AND/OR ADVANTAGES

PDE5 inhibitors have demonstrated utility in reducing pulmonary vascular resistance (PVR) and improving ventricular performance in patients with pulmonary hypertension and myocardial dysfunction. These characteristics make PDE5 inhibitors, particularly a long acting compound such as udenafil, an appealing therapy to consider for patients with the Fontan circulation in which the maintenance of low PVR and normal myocardial function are crucial determinants of long-term clinical outcomes. The phase I/II clinical trial (NCT02201342) demonstrated that udenafil was safe and well tolerated at all studied doses in male and female adolescents who had undergone Fontan palliation.<sup>1,5</sup>

### DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Udenafil does not currently have Marketing Authorisation in the EU/UK for any indication.<sup>6</sup>

Udenafil is in phase II/III development for pulmonary arterial hypertension.<sup>7</sup>

- Udenafil is a designated orphan drug in the EU in December 2016 for the treatment of functional single ventricle congenital heart disease<sup>8</sup>
- Udenafil is a designated orphan drug in the USA in August 2015 for the treatment of single ventricle congenital heart disease with Fontan physiology<sup>9</sup>

### DISEASE BACKGROUND

Congenital heart disease is a general term for a range of birth defects that affect the normal way the heart works.<sup>10</sup> Like most congenital heart defects, there is no known cause for single ventricle defects.<sup>11</sup> Single ventricle defects are rare disorders that a child is born with affecting one lower chamber of the heart. The chamber may be smaller, underdeveloped, or missing a valve. There are several types of single ventricle defects. These include:<sup>12,13</sup>

- tricuspid atresia
- hypoplastic left heart syndrome (HLHS)
- mitral valve atresia (usually associated with HLHS)
- single left ventricle
- double inlet left ventricle (DILV)
- double outlet right ventricle (DORV)
- pulmonary atresia with intact ventricular septum (PA/IVS)
- Ebstein's anomaly
- atrioventricular canal defect (AV Canal)

Single ventricle defects can cause children to become cyanotic (turn a blue colour), since a mixture of oxygen-poor (blue) and oxygen-rich (red) blood vessels leaves the heart and goes to the body. Just how much oxygen or how little oxygen depends on the type, location and severity of the defect. Some children will only be mildly cyanotic, while others will not have enough oxygen in the blood to meet the body's needs and will need early treatment.<sup>13</sup> Other symptoms of single ventricle defects include: shortness of breath (dyspnoea), fast breathing or breathlessness, poor feeding, lack of energy (lethargy), weak pulse, and pounding heart.<sup>11</sup>

Many patients have survived three to five decades after single ventricle surgery in childhood. Many of these patients are highly functional, with good activity levels. However, some patients with single-ventricle defects do have health problems, which may include:<sup>12</sup>

- Rhythm problems, generally fast heart rate (tachycardia, supraventricular tachycardia, atrial flutter) or slow heart rate.
- Fluid retention, particularly in the abdomen and lower extremities. Some adults may develop varicose veins after the operation.
- Greater risk of weakening and failing heart muscle when there is only one ventricle.
- Blood clots inside the heart that may require anticoagulation therapy.

The occurrence of these complications and need for hospitalisation influences the life expectancy and emotional, behavioural, and psychosocial condition of these patients. Additionally, the patients' quality of life (QOL) and perception of their health status also influence treatment outcomes. Therefore, patients' perceived physical and mental health should be taken into account to optimise treatment.<sup>14</sup>

### CLINICAL NEED AND BURDEN OF DISEASE

Congenital heart disease is one of the most common types of birth defect, affecting up to 8 in every 1,000 babies born in the UK.<sup>10</sup> As of 2016, functional single ventricle congenital heart disease affected approximately 0.3 in 10,000 people in the European Union.<sup>8</sup> Reports suggest that the UK single ventricle population is approximately 1,040 adults and 1,700 children, with an expected increase in adult numbers by 60% within the next decade.<sup>15</sup>

Operative mortality of the Fontan procedure has steadily decreased and is currently <2%.<sup>16,25</sup> Freedom of death or transplantation in the early survivors of a population of Fontan patients born

before 1985 was reported as 93.7%, 89.9%, 87.3%, 82.6% and 69.6% at 5, 10, 15, 20 and 25 years, respectively.<sup>17</sup> Successful management of single ventricle defects has been possible only over the past few decades and doctors continue to follow these children to better understand the long-term outcomes.<sup>11</sup>

## PATIENT TREATMENT PATHWAY

### PATIENT PATHWAY

In many cases, congenital heart disease is diagnosed during pregnancy. However, a diagnosis may sometimes only be confirmed after the birth. Shortly after birth, babies with single ventricle defects are given an injection of medication called prostaglandin. This encourages the mixing of oxygen-rich blood with oxygen-poor blood. The condition will then need to be treated using a 3-stage procedure.<sup>18</sup>

The first stage is usually performed during the first few days of life. An artificial passage known as a shunt is created between the heart and lungs, so blood can get to the lungs. This improves cyanosis. Some children with tricuspid atresia have too much blood flowing to the lungs. They may need a different type of surgery, called pulmonary artery banding, to decrease blood flow to the lungs. This is important to protect the lung blood vessels. A small number of children have just the right amount of blood going to the lungs and do not require an initial operation.<sup>12,18</sup>

The second stage is performed between 3 to 6 months of age. The large vein from the upper half of the body (the superior vena cava) is connected to the lung arteries in a procedure called a bi-directional Glenn operation. This connects veins that carry oxygen-poor blood from the upper part of the body directly to the pulmonary artery. This allows blood to flow into the lungs, where it can be filled with oxygen.<sup>12,18</sup>

The final stage is usually performed between 18 to 36 months of age. It involves connecting the large vein from the lower half of the body (the inferior vena cava), as well as the veins from the liver, to the lung arteries, effectively bypassing the heart. This is known as the Fontan procedure, or Total Cavopulmonary Connection (TCPC).<sup>12,19</sup>

Children who have undergone a Fontan procedure for palliation of a functional single ventricle are at risk for medical complications and require lifelong specialist care. Short-term morbidity includes persistent pleural drainage, extended length of stay in hospital, prolonged mechanical ventilation and need for inotropic support, as well as acute thrombotic events. Long-term problems also include thrombotic events, venous hypertension, arrhythmias, and congestive heart failure.<sup>19, 20</sup>

Currently, no treatment can completely correct single ventricle defects and restore normal circulation. Patients with Fontan palliation of single ventricle heart disease may experience a range of complications.<sup>11</sup> Scientific evidence on which to base prescription decisions for the Fontan population is lacking.<sup>21</sup> There is no consensus on the optimal drug treatment for the prevention of failure of the Fontan circulation.<sup>22</sup>

### CURRENT TREATMENT OPTIONS

- The empiric use of anticoagulant and antiplatelet agents has been based on the well-documented risk of thrombotic complications for Fontan patients, but these complications still occur for patients receiving such preventive therapy, and neither retrospective nor prospective studies have proven efficacy.<sup>21,23</sup>

- Angiotensin converting enzyme inhibitors (ACEi) may improve vascular endothelial function but not cardiac output or exercise capacity.<sup>24</sup> Bosentan, sildenafil, and iloprost may improve exercise capacity at the short term. However, larger and longer placebo-controlled studies are needed to evaluate efficacy and safety of drug therapies in the prevention and treatment of failure of the Fontan circulation.<sup>21</sup>
- A heart transplant may be recommended for a small number of patients but is limited by the lack of available hearts for transplantation.<sup>18</sup> The main indications for transplantation are heart failure, intractable arrhythmias, protein-losing enteropathy, and plastic bronchitis, which is another rare complication of congenital heart defects, particularly in Fontan patients.<sup>25</sup>

## PLACE OF TECHNOLOGY

If licensed, udenafil may offer an additional treatment option for adolescent (12-18 years old) patients for the management of congenital heart disease after Fontan palliation who currently have few effective therapies available.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	FUEL, NCT02741115, PHN-Udenafil-02, U01HL068270; aged 12-18 years; udenafil vs placebo; phase III	FUELExten, NCT03013751, PHN-Udenafil-03, U01HL068270; aged 12-18 years; udenafil; phase III extension
<b>Sponsor</b>	Mezzion Pharma Co. Ltd	Mezzion Pharma Co. Ltd
<b>Status</b>	Ongoing	Ongoing
<b>Source of Information</b>	Trial registry <sup>3</sup> , manufacturer	Trial registry <sup>4</sup> , manufacturer
<b>Location</b>	USA, Canada, and Republic of Korea	USA, Canada, and Republic of Korea
<b>Design</b>	Randomised, placebo-controlled, double-blind, parallel assignment	Single group assignment, open label
<b>Participants</b>	n=400; aged 12-18 years; males and females with Fontan physiology	n=300 (planned); aged 12-18 years; males and females with Fontan physiology who participated in the FUEL trial or, if they did not participate in FUEL, those who are 12 to less than 19 years of age at enrolment; current anti-platelet or anticoagulant therapy
<b>Schedule</b>	Randomised to udenafil one tablet twice daily for 26 weeks; or placebo one tablet twice daily for 26 weeks. Dosing specifics were not provided on the trial registry.	Udenafil administered for 52 weeks. Dosing specifics were not provided on the trial registry.
<b>Follow-up</b>	Scheduled clinic visits throughout the 26 week dosing and 90 days post dosing for safety follow-up. <sup>a</sup>	Scheduled clinic or phone visits throughout the 52 weeks of dosing. <sup>a</sup>
<b>Primary Outcomes</b>	<ul style="list-style-type: none"> <li>• Change in Exercise Capacity [Time frame: Baseline to 26 wks]</li> </ul>	<ul style="list-style-type: none"> <li>• Safety (Adverse Events) [Time frame: 52 wks]</li> </ul>

<sup>a</sup> Information provided by company

	The change in exercise capacity (as measured by maximal VO2 at maximum exercise effort) from baseline to 26 weeks (or study completion)	Adverse Events
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>Change in Myocardial Performance Index (MPI) [Time frame: Baseline to 26 wks] The change in the myocardial performance index (MPI) from baseline to 26 weeks determined by velocities obtained from blood pool Doppler assessment of the inflow and outflow tract of the dominant ventricle.</li> <li>Change in log-transformed reactive hyperemia index (lnRH) [Time frame: Baseline to 26 wks] The change in log-transformed reactive hyperemia index (lnRHI) from baseline to 26 weeks as measured by pulse amplitude tonometry (PAT) testing using the EndoPAT® device.</li> <li>Change in Level of Serum serum brain-type natriuretic peptide BNP [Time frame: Baseline to 26 wks] Change in Level of Serum serum brain-type natriuretic peptide BNP from baseline to 26 weeks.</li> </ul>	<ul style="list-style-type: none"> <li>Exercise (Change in maximal oxygen consumption) [Time frame: 52 wks] Change in maximal oxygen consumption.</li> <li>Echo (Change in myocardial performance Index) [Time frame: 52 wks] Change in myocardial performance Index</li> <li>Endothelial function (Change in log-transformed Reactive Hyperemia Index) [Time frame: 52 wks] Change in log-transformed Reactive Hyperemia Index</li> <li>Function Health Status (Change in full scale Peds QL) [Time frame: 52 wks] Change in full scale Peds QL</li> <li>Biomarkers (Change in serum BNP level) [Time frame: 52 wks] Change in serum BNP level from baseline to end-of-study</li> </ul>
<b>Key Results</b>	-	-
<b>Adverse effects (AEs)</b>	-	-
<b>Expected reporting date</b>	Primary completion date reported as December 2018; study completion date reported as March 2019.	Primary and study completion dates are reported as February 2019.

## ESTIMATED COST

The cost of udenafil is not yet known.

## ADDITIONAL INFORMATION

Mezzion Pharma Co. Ltd

Mezzion Pharma Co. Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other

sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

## 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
- NICE interventional procedures guidance. Balloon dilatation of systemic to pulmonary arterial shunts in children (IPG77). July 2004

### NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/2014 NHS Standard Contract for Pulmonary Hypertension Service (Children). E05/S(HSS)/a
- NHS England. Service Specification: Cardiothoracic Transplantation Service (Paediatrics). 170013/S
- NHS England. Commissioning Operations: Congenital Heart Disease Standards & Specifications, 2016

### OTHER GUIDANCE

- The Society of Thoracic Surgeons. The Patient Guide to Heart, Lung, and Esophageal Surgery: Single Ventricle Defects. 2017<sup>11</sup>

## REFERENCES

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<sup>12</sup> American Heart Association. *Single Ventricle Defects*. Available from: <http://www.heart.org/en/health-topics/congenital-heart-defects/about-congenital-heart-defects/single-ventricle-defects> [Accessed 28 September 2018]

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