Perspectives of Patients and Caregivers on Living with Fontan Circulation and Treatment with Udenafil

A Summary of Patient Experiences and Preferences by:

MENDED LITTLE HEARTS

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Submitted as patient experience data for consideration pursuant to section 569C of the Federal Food, Drug, and Cosmetic Act to the FDA Center for Drug Evaluation and Research’s Division of Cardiology and Nephrology.
On behalf of the over 70,000 people in the United States living with Fontan Circulation, and their families, we request that the U.S. Food and Drug Administration consider and incorporate our experiences, perspectives, and preferences in its review of the New Drug Application (NDA) for Udenafil submitted by Mezzion Pharmaceuticals. Each year, there are 1062 Fontan operations performed each year (15,934 from 2001 to 2014) with a decrease in mortality and post-operative complications. Due to the decrease in mortality, there is an increase focus on quality of life for these patients and to increase survival age. For this reason, we are writing about Udenafil today.

FDA has repeatedly signaled the importance of incorporating patient input into drug development and review, including to us directly by Dr. Norman Stockbridge, Director, Division of Cardiology and Nephrology who invited such information to be provided specifically within the context of the Udenafil NDA. This is especially critical in rare diseases where there are inherent challenges and limitations in designing, conducting, and, as a result, interpreting clinical trials. The 21st Century Cures Act created a framework for FDA to consider the patient perspective by considering our input as “patient experience data.”

About Our Organization
The Mended Hearts, Inc. is the nation’s premier peer-support non-profit organization for people of all ages living with cardiovascular disease, their caregivers, and their families. Since 1951, we have served millions across a wide range of heart diseases by providing support and education, bringing awareness to issues that those living with these conditions face and advocating to improve quality of life across the lifespan.

In 2004, we recognized a unique need to provide hope and support to “the littlest heart patients of all” and their families, so the Mended Little Hearts® program was created. Mended Little Hearts provides hope and support, creating awareness and being a strong voice for children born with heart conditions and their families, including those facing the serious daily challenges and long-term consequences of living with Single Ventricle Heart Disease and Fontan Circulation.

Currently, Mended Hearts® has approximately 71,000 members across the lifespan, about 19,000 of whom are parents and family members of children born with heart disease and the children themselves.

Our Interest in Udenafil
About 40,000 babies are born each year with congenital heart defects, and 25% will need surgery or other medical intervention to survive. Single ventricle congenital heart defects remain the most difficult to treat and there is no cure. The Fontan surgical procedure allows single ventricle patients to survive, but it does not fix the heart, and there are many complications that can occur with the Fontan anatomy.
For too long, there have been no approved treatment options to help make life better for children and adults with Fontan circulation. When we found out about the Fontan Udenafil Exercise Longitudinal (FUEL) trial, we were very optimistic to have research dedicated to improving the lives of our children. Many of our member families participated in FUEL and the open label extension (OLE), and the future of this potential treatment option is of great interest to us. Having a medication with the potential to help children and young adults living with Fontan anatomy gives us hope for a better future.

The Clinical Trials Show Udenafil Provides Important Treatment Benefits

The results of the FUEL trial and OLE extension have only bolstered our optimism for the potential for a therapy to improve the lives of our children. FUEL measured the effect of Udenafil using several indicators of exercise capacity in 400 Fontan patients, an incredible enrollment number for our community. The primary measure, the maximum amount of oxygen consumed by the body during an exercise test (max VO2), showed an increase of 44.40 mL/min for those taking Udenafil but a decline (-3.65 mL/min) for those on placebo, a result that just missed being statistically significant (p=0.071). However, several related measures of the body’s ability to use oxygen during exercise as well as the functioning of the heart showed a similar improvement for those taking Udenafil but were statistically positive.

Many of the young people who participated in the FUEL trial were able to continue into the OLE trial, during which all participants received Udenafil. Over an even longer time period (one year for the OLE compared to six months for FUEL), both participants who continued to receive Udenafil and those receiving it for the first time showed improvement in exercise capacity. From the Fontan patients in our own families and in our community, we know the limitations that living with Fontan Circulation puts on our loved ones’ ability to engage in the activities of daily life, let alone limitations to their ability to play and enjoy the physically active parts of life. We also know that those limitations are signs of long-term consequences of Fontan. Access to therapies that will help improve physical capacity for those living with Fontan Circulation would provide a way to significantly improve our loved ones’ quality of life.

Individual Patient Experiences on Udenafil Provide Important Context for Evaluating the Trial Results

Beyond the results of the studies, which provide important metrics of meaningful treatment benefits, it is important to also consider that the young people with Fontan circulation who received Udenafil in FUEL/OLE experienced it as individuals, not as a group with a mean response and a corresponding p-value. A complete view of the data should account for these individual-level experiences where many of our children (and adult patients) experienced tangible benefit from the medication in their daily lives. So, as a supplement to the existing NDA and to provide context to your ongoing review, we would like to provide the FDA with additional perspective on how living with Fontan circulation affects us and how important it is to have a potential treatment option that may help maximize quality of life. In an effort to provide the patient perspective, we reached out to Dr. Norman Stockbridge, and he indicated that providing an advocacy supplement to the Mezzion submission would be appropriate.
Note that this submission includes just a few direct quotes from Fontan patients and their caregivers. We, however, are committed to soliciting additional direct input from our full membership to further inform your regulatory decision on Udenafil, so we expect to follow-up with you with additional input in the near future.

Our goal is to assure that the patient community voice is heard during the FDA review of Udenafil.

**Understanding the Challenges of Living with Fontan Circulation**

Jodi Smith Lemacks, Esq. is our National Program Director at The Mended Hearts, Inc. and is the mother to Joshua, a teen living with Fontan circulation. Jodi’s son Joshua was a participant in FUEL/OLE. With respect to living with Fontan circulation, Joshua has said, “I look for every opportunity I can to get healthier and live the life I should. I have participated in the FUEL trial because my mom and I felt like the medicine might help me be healthier and possibly even live longer. I lost my best friend at age 12 to this heart disease, so I feel strongly about living my life to the fullest.”

Like Joshua desires, every child and adult with Fontan circulation should be able to live the life they want, but the reality is that their reduced cardiac function affects virtually all aspects of their daily lives and makes it challenging to be positive about their future. Below are some specifics about how living with Fontan affects our children and our families.

**Patients Bear the Burden of Symptoms and Health Effects**

Many children and young adults living with the Fontan circulation face limitations, especially as their bodies get bigger and their hearts have to work harder to pump blood to the body. With the Fontan, the heart has only one pumping chamber versus two in a normal heart. Blood goes to the heart passively into the lungs and then back into the heart where the one ventricle pumps it to the body. As a result, the blood coming back into the heart from the body is working against gravity and can get congested in the veins. This may lead to, at worst, liver damage as the hepatic vein gets congested and heart failure. At best, patients with the Fontan may have leg and feet problems, more difficulty healing from wounds or infections, less stamina, get out of breath faster than their peers, and have difficulty with strenuous activities. All of these consequences of the Fontan have been shown to also lead to more issues with anxiety and depression and attention deficit disorder and other learning issues. Any medication that improves getting oxygenated blood to the body and back to the heart has the potential to improve any or all of these consequences.

**Patients Experience Significant Activity Limitations**

As stated above, our children with Fontan circulation reach adolescence, the limitations of their unique hearts become even more evident. These limitations include decreased ability to exercise or even be active, increased need for heart failure medication (and other medications), hospitalizations, and potential damage to other organs (especially the liver). When children
can’t stay active, this negatively impacts their heart health which can compound the congenital heart issues already present. In fact, children with congenital heart defects get acquired heart disease at the same rates as children without congenital heart defects.

One parent told us that their child’s school sent home a flyer about every child “running a marathon.” This was over a period of time where they children would track their distance ran. This mother watched her child get so excited but knew that this was not possible for her child in this time period. They had to come up with another plan, which was heartbreaking to the mother and made the child feel different from her peers.

In addition to the health impact of their activity limitations, the social impact is also very important. Many Fontan patients can’t keep up with their peers at an age where this matters to them more than ever.

Many parents have shared the need for finding sports their child can do. When they are younger and sports are less competitive, children who have the Fontan are often able to do many different sports, but as they get older, they often cannot do sports that require lots of running like soccer and basketball. One father told us that his son played baseball from the age of 4 through Middle School. When he got to high school, he went to the first day of pre-season conditioning and ended up vomiting and unable to complete it. His son loves baseball, but because of his Fontan anatomy, he is unable to play now and there are no recreational leagues in their area for children high school ages.

Even children in activities such as marching band face issues. Often, there are some instruments that children who have the Fontan have difficulty with or cannot play at all. One parent told us that her daughter wanted to be in marching band, but she could only play certain instruments and carrying the instruments and marching in a band uniform was too much for her. They had to come up with a plan for her so she could participate, but she was embarrassed to need this help.

Fears for the Future Living with Fontan Circulation
The average life expectancy for people who have had Fontan surgery is 35 to 45 years, most often due to congestive heart failure but also to sudden cardiac death, liver disease, blood clots, or valves failing to work. Some of our children, like Joshua, have already experienced the death of close friends who also had Fontan, and they struggle with anxiety and depression as a result of having to grapple with their own early mortality. No child or caregiver should have to live with this fear or the mental health aspects related to it.

Hopelessness and Preferences for Futures Treatments
Our fears for the future are compounded by a feeling of hopelessness given that there are no approved treatments to improve symptoms, functioning or prognosis for our children with Fontan circulation. Surgery is not a cure. And while we are waiting for a cure, we need medications like Udenafil that can help us stay healthier longer.
If a treatment could even slow the progression of the underlying condition over time, such that the gradual decline in quality of life could be delayed, that would be meaningful to us. While we would hope for a treatment that substantially reverses the condition or cures it, we do not need that type of benefit for a treatment to be meaningful today. Even if there was some uncertainty about whether a treatment would help everyone who took it or whether the benefits experienced now will translate to long-term benefits, we would prefer to have the option for that potential to benefit.

**Sharing Our Experiences with Udenafil in FUEL/OLE**

While everyone’s experience is unique, our own National Program Director, Jodi (mother of Joshua) has commented that, “Udenafil is truly an answer to our prayers and has been life-changing for my family and for so many other families like mine.” Several families, like Jodi’s, told us that they had been hoping for something to come along that would help their child for years, and Udenafil gave them hope. Below are some of the ways many parents and patients have reported as their experience while taking Udenafil while enrolled in FUEL/OLE.

**Patients Report Increased Activity in Daily Life**

Families have reported functional benefits with Udenafil. Most commonly, they share that their loved one is able to engage in more strenuous physical activity as well as an increased range of activities. For some adolescents and young adults, this has meant being able to participate in solo or group activities where they previously needed to stay on the sidelines. One parent told us her child wanted to be on the swim team but was really struggling to complete practice before Udenafil. Udenafil did not make her son a champion swimmer, but he could participate in swim meets and even won some ribbons. This made them both very happy.

**Treatment Today Provides Hope for Future Benefits**

People with Fontan circulation and their families desperately seek a sense of hope for their future. Having access to a potentially beneficial medication means being able to take positive action every day, even if there is uncertainty in the extent of the benefit in the long run. Yet, knowing that their labs are stable or improving provides hope that the treatment may be changing the course of their condition. Even though it’s years down the road, they know that every extra day that their children can maintain their activity level and stay healthier means another day they can play and engage in the activities of daily life.

**In Conclusion**

Congenital Heart Defects are the number one type of birth defect in the United States, and those born with a single ventricle have limited options of treatment. The need for options is vital to the long-term outcomes of our children. People with Fontan circulation live every day with significant burdens of their condition, with the symptoms and health effects limiting their ability to function and participate in activities in their lives, all the while fearing the known future decline. Patients taking Udenafil and their caregivers report a contrast in their current experience and possess long-term hopes for the future. Given the lack of approved treatments for Fontan circulation patients, we ask that FDA consider these experiences and preferences as
you have the opportunity to provide an alternative to that status quo. Even if there is uncertainty in the degree of ultimate clinical benefit, we desire even the potential for important benefit given the current absence of any treatment option.

Please read and take into consideration the accompanying initial packet of testimonials from patients, and caregivers living with Fontan circulation.

We appreciate that you are listening to the patient voice throughout this process and appreciate your time and consideration. We look forward to engaging with you all in the future and providing more testimonials in the coming weeks for consideration.

Sincerely,
Andrea Baer
Executive Director
The Mended Hearts, Inc.
https://mendedlittlehearts.org/