

DYSAUTONOMIA INTERNATIONAL



AWARENESS



ADVOCACY



ADVANCEMENT

December 11, 2012

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Room 2217
Silver Spring, MD 20993

Director Dr. Janet Woodcock
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Re: Droxidopa, Midodrine & PDUFA V

Dear Drs. Hamburg and Woodcock,

We are writing to you today on behalf of thousands Americans suffering from Neurogenic Orthostatic Hypotension (NOH). Our organization, Dysautonomia International, advocates on behalf of people living with disabling disorders of the autonomic nervous system, one of which is NOH.

The FDA has two regulatory matters pending regarding two drugs that treat NOH, Midodrine and Droxidopa. Dysautonomia International strongly encourages FDA to take whatever steps necessary to retain US approval of Midodrine, so that the 100,000 Americans who rely on this drug on a daily basis, simply to sit or stand up, can continue to receive this life changing medication. Dysautonomia International also requests the FDA to adhere to the recommendations of its own advisory committee and approve Droxidopa, as soon as possible. The patients who can benefit from these drugs have no other options. They face a devastating medical condition that impacts every moment of their life. Imagine the inability to sit upright without fainting or the inability to stand without losing one's vision due to a severe drop in blood pressure. The involuntary bed rest that would result is no way to live your life, and prolonged bed rest leads to increased co-morbidities and mortality in these patients as well. It is imperative that physicians treating NOH patients have access to as many tools as possible that may help alleviate their patient's condition.

Who has NOH?

NOH is generally a consequence of a serious underlying neurological disorders.

Virtually all 50,000 patients in the US with Multiple System Atrophy (MSA), a fatal neurodegenerative disorder causing severe autonomic dysfunction, suffer from NOH. MSA patients are typically adults, in their 40s and 50s, and they live an average of 5-10 years after the onset of their first symptoms. The disease progresses in such a way that the patient usually ends up in a wheelchair or bed-bound due to the increasing severity of their orthostatic hypotension. The longer MSA patients are able to remain upright, and not bed-bound due to severe orthostatic hypotension, the better their quality of life for the short time they have left. Being confined to bed also increases the risk of pulmonary embolisms, and severe respiratory infections, which is the leading cause of death in MSA patients. While there is no cure for MSA at this time, drugs that can minimize the severity of NOH are the best hope for a better quality-of-life and perhaps a somewhat longer life in MSA patients at this time.

NOH is also seen in patients with Pure Autonomic Failure (PAF). It is unknown how many individuals in the US suffer from PAF, but our organization has many members who have been diagnosed with it. PAF is a slower neurodegenerative disorder than MSA, and its primary symptom is NOH. Patients with PAF may live a normal lifespan, but without drugs like Midodrine and Droxidopa to combat their NOH symptoms, their life would have to be lived from a reclined position. PAF patients cannot maintain their blood pressure in response to gravitational forces. Sitting up or standing often results in syncope. This can lead to repeated concussions, broken bones, or worse.

NOH is also seen in patients with Diabetic Autonomic Neuropathy and peripheral autonomic neuropathies caused by autoimmune diseases such as Sjogren's Syndrome, Lupus, Celiac Disease and Autoimmune Autonomic Ganglionopathy. In these patients, a damage to small fiber autonomic nerves leads to a decrease in the ability of blood vessels to constrict in response to upright posture, resulting in significantly decreased blood pressure, and if the patient remains in the upright position long enough, eventually syncope. For some of these patients, syncope can occur even in the sitting position. Patients with severe forms of autonomic neuropathy are at increased risk for falls and injuries when standing up, and in some cases, these patients will have orthostatic hypotension so severe that they become confined to bed. Being bedridden leads to deconditioning and all of the co-morbidities that accompanies it.

Drugs like Midodrine, and potentially Droxidopa, can help all of these patients remain upright and live a healthier and more normal life.

Midodrine

Dysautonomia International is extremely concerned about FDA's possible revocation of Midodrine approval in the US. There are 100,000 Americans who regularly fill prescriptions for Midodrine. Some have NOH. Many others have Postural Orthostatic Tachycardia Syndrome (POTS), another autonomic disorder that our organization is focused on.

Experts at Vanderbilt University's Autonomic Dysfunction Center have estimated that 500,000 to 1,000,000 Americans have POTS, mostly young women of childbearing age. A noted Mayo Clinic pediatric cardiologist estimates that 1 in 100 teenagers are now developing POTS before adulthood. Mayo Clinic's research indicates that 57% of POTS patients have a peripheral autonomic neuropathy. This is often referred to as the "neuropathic" subtype of POTS, as there are several subtypes. Researchers from New York Medical College have demonstrated that Midodrine is particularly helpful in treating the neuropathic subtype of POTS, which is associated with a peripheral autonomic neuropathy. While POTS is not believed to be a progressive neurodegenerative disorder like MSA or PAF, the quality-of-life of POTS patients has been described by doctors as similar to what is seen in COPD or congestive heart failure, and most POTS patients are teenagers and young women. Midodrine helps many of these young patients get back to the prime of their life. They should be at school dances and going off to college, getting married and having their first children. Without Midodrine, many of them would not be able to sit upright or stand, which leads to severe deconditioning and all of the co-morbidities associated with it. If you remove Midodrine from the market, this will result in tens of thousands of young women not being able to live a productive life. They will become bedridden, homebound, more of them will end up on Social Security Disability and they will live a very difficult life. Please consider the quality-of-life and health of the patients who rely on Midodrine and have no other options before making any decision to withdraw this essential drug from the market.

While Midodrine is helpful to many NOH and neuropathic POTS patients, not all NOH or neuropathic POTS patients can tolerate Midodrine. The side effects that some patients experience, including bradycardia, severe chills and goosebumps, unrelenting itchy scalp, and supine hypertension, and the short acting nature of the drug, make it a less than ideal for all patients. This is why having a second drug that combats NOH is important. Patients and their physicians need options.

Droxidopa

Droxidopa is a promising new drug for the treatment of NOH. While we understand the FDA's role is to ensure the safety of a new drug, and to protect the American public from snake oil salesmen selling medications that do not work, Droxidopa has benefitted a sizable percentage of the NOH patients who have been lucky enough to try it in the US. We hear positive things on the dysautonomia patient forums, chat groups and websites from those who have tried it. Other patients who have NOH are excited to have a potential new treatment tool to help them.

Relationship to FDA's PDUFA V Patient Focused Drug Development Initiative

Our organization heard about FDA's recent comment period on the Prescription Drug User Fee Act V Patient Focused Drug Development (Docket ID: FDA-2012-N-0967). Unfortunately, we only learned about this a few days before the comments were due and many of our board members were in communities damaged by Hurricane Sandy, so we were not able to get our submission to the FDA in time. However, we would like FDA to know that we were going to propose autonomic disorders as a whole, as a category of illness that would benefit from more patient input on how to fairly measure research endpoints. It is medical tradition to avoid subjective analysis from patients as part of drug efficacy studies, but we think that autonomic disorders are so complex and so poorly understood, that allowing more subjective considerations of symptom improvement may be appropriate. Our collective medical knowledge about how these conditions impact the entire body is really only scratching the surface. Looking at endpoints such as improvements in the ability to sit upright, to get out of bed

unassisted, ability to walk, hours the patient is able to concentrate, read and speak clearly, and hours the patient is able to socialize or engage in work or school activities, hours that the patient is free from dizziness and lightheadedness, are all relative to the patients quality-of-life. These are not easily measured in research settings, but these are the improvements dysautonomia, and specifically NOH, patients are looking for when they try a new drug.

Since the FDA's current objections to Droxidopa are based on an efficacy concern, specifically that one of the study sites disproportionately contributed to the study success, which prevented the FDA from accepting a single study alone as adequate evidence of effectiveness, we ask the FDA to take into consideration the totality of the circumstances and all of the data available on Droxidopa, not just one potential problem with one study location. This situation poses an overall policy question for FDA – if a drug helped thousands of people living with a devastating and rare medical condition that is poorly understood, but not enough people to meet formal “statistical significance” standards, would it be fair for FDA to prevent patients who did benefit from the drug from receiving it? In practice, if a drug does not help a patient, or if the side effects are not worth the improvement felt by the patient, most likely the patient will stop taking the drug and it will fall out of favor with practitioners. This patient population is not generally getting their medications from the local family doctor. They are usually being treated by an expert in autonomic disorders or neurodegenerative disorders, who is more than capable of determining whether the drug is helping the patient or not. We think there is enough data supporting Droxidopa's safety and efficacy to allow physicians the right to prescribe this drug to their patients. Let physicians decide, on a case by case basis, whether Droxidopa is the right drug for their patient, and whether their patient is experiencing enough of a benefit from it to continue therapy.

We also want the FDA to understand that autonomic disorders such as MSA, autoimmune neuropathies and NOH are notoriously difficult to treat. Each patient tends to present with a slightly different manifestation of the illness. As these neurological diseases progress, a drug that may have helped during the first few years of the illness may not longer be of much benefit. It is possible that the rigorous standardized testing that FDA requires to establish efficacy is not an accurate or fair measure of benefit that patients will see in their day to day life. For example, if increased blood pressure is used as an endpoint, we know from experience with this patient population that one person with a blood pressure of 120/80 can feel lightheaded and temporarily lose their vision due to poor cerebral blood flow, while another person with a blood pressure of 90/40 can feel fine. Blood pressure measured on the arm is not a precise indicator of proper autonomic control of blood flow throughout the body, and particularly to the brain.

We also want to alert the FDA to other problems faced by those looking to study the dysautonomia patient population. First, many of the patients who need these drugs the most are too sick to travel. Autonomic disorders do a lot more to the body than just causing NOH. Many dysautonomia patients have problems with motion sickness in cars, possibly due to an imbalance in the autonomic nerves involved in regulating the vestibular system. PAF patients tend to have problems with high altitude, making plane travel or cross-country road travel problematic. Some dysautonomia patients have severe gastric motility problems, requiring feeding tubes, TPN or constant access to the restroom, while others regularly receive infusions of IV saline to help improve blood volume and mitigate low blood pressure. Some dysautonomia patients cannot leave the reclined position, and they use heavy, large reclining wheelchairs. It is very hard for many of these patients to get in a car or plane to travel somewhere to participate in a research study. This makes it very difficult to find enough of these patients willing and able to participate in drug studies.

Compounding this problems, many autonomic disorders are relatively rare. There are few physicians and researchers with solid autonomic expertise in the US. Those that do exist are overwhelmed with a large number of patients trying to get into their practice for treatment. Many of the autonomic experts we have spoken with do not want to engage in research on behalf of a pharmaceutical manufacturer – not because they think a new drug is a bad idea – but because they don't want to have any conflicts of interest or even an appearance of one, or they are simply too busy trying to keep up with their current patients.

We have reviewed the research on Droxidopa that is publicly available. We have heard from our patients and their caregivers. We think there should be no further delay in making Droxidopa available to the NOH patient population and respectfully request you use the tools made available to you in PDUFA V to find an appropriate regulatory path forward for Droxidopa.

Conclusion

Thank you for the opportunity to comment upon these matters. We look forward to FDA's decisions on Droxidopa and Midodrine. If our organization can be of any assistance to you in making your decisions or gathering input from patients, please feel free to contact us any time at (631) 874-2384.

Sincerely,

The Board of Directors of Dysautonomia International

By:



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