

September 8, 2010

Robert Temple, M.D.
Director
Office of Medical Policy
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: Midodrine hydrochloride

Dear Dr. Temple:

On behalf of the American Society of Nephrology (ASN), please accept this letter of support for the Food and Drug Administration's decision to maintain approval for Midodrene Hydrochloride (Midodrine HCl). We urge you to take into consideration the negative implications for patients of withdrawing approval for Midodrine HCl when considering a final determination on the medication in the coming months. ASN is a not-for-profit organization of 11,000 physicians and scientists dedicated to promoting excellence in the care of patients with kidney disease. Foremost among ASN's concerns is the preservation of the most appropriate treatment options for patients with kidney disease.

Recognizing the prerogative of the Food and Drug Administration (FDA) to withdraw approval of medications that do not meet established guidelines, the society respectfully urges FDA to consider allowing the continued use of Midodrine HCl. Today, Midodrine HCl is widely recognized among clinicians as the most appropriate, and sometimes the only, treatment option for patients with certain diseases relating to hypotension. For example, removing this drug would leave patients and providers with no clear alternative for management of dialysis-related hypotension.

Autonomic dysfunction is common among patients with kidney disease, particularly because uremia and diabetes both predispose to autonomic neuropathy. Sympathomimetic agents such as Midodrine HCl have been useful options in the armamentarium of treatment options for hypotension for renal patients for many years. Among these agents, Midodrine HCl appears—based upon decades of clinical experience—to be effective as well as relatively free of side-effects. Today, it remains widely used to treat dialysis-related hypotension and hypotension related to autonomic dysfunction in kidney patients.

The society understands that FDA's primary focus is the use of Midodrine HCl for the treatment of orthostatic hypotension. However, the society would like to illuminate the use of Midodrine HCl in other patient populations; namely, in end-stage renal disease (ESRD) patients who undergo maintenance hemodialysis. Symptomatic hypotension requiring treatment occurs frequently during hemodialysis. The incidence is variable, but the literature suggests it is approximately 15%. Considering that over 350,000 patients are on chronic hemodialysis in the United States alone

— and each patient undergoes treatment on average of three times per week—the number of patients experiencing symptomatic intradialytic hypotension episodes is significant. It is important to weigh the concern of these patients when considering the future of Midodrine HCl.

The large body of literature on symptomatic intradialytic hypotension clearly indicates that the problem is common, severe and complex. Similar to the general population with postural hypotension, autonomic dysfunction is an important consideration in dialysis patients, because the prevalence and severity of such symptoms are much more pronounced in this patient population. During dialysis, rapid fluid removal (and consequently, the sudden decrease in intravascular volume) compounds the problem further, eliciting a sympathetic withdrawal response. This detrimental phenomenon has been clearly demonstrated by assessment of heart rate and microneurography (Converse RL, N Engl J Med 327:1912-1918, 1992).

Besides of the acute symptoms patients with symptomatic intradialytic hypotension—including headache, muscle cramps, chest pain, dizziness and loss of consciousness— intradialytic hypotension also necessitates decreasing the ultrafiltration (fluid removal) rate. Often the effect of reducing fluid removal or interrupting the dialysis procedure is that the target volume and solute removal cannot be achieved, and the treatment is inadequate.

Importantly, administration of oral Midodrine HCl immediately before the hemodialysis session can mitigate many of the symptoms, and resulting treatment interruptions, described above. Nephrologists have widely employed Midodrine HCl to prevent or decrease symptomatic intradialytic hypotension for years, and in recent years, its use has increased. Several original publications have shown its effectiveness in this setting. The specificity of Midodrine HCl for the alpha-1 adrenergic receptor limits its side effects, as confirmed by clinical experience. Moreover, the European Best Practice Guidelines include the administration of Midodrine HCl as one of the treatment options for intradialytic hypotension. The extensive experience of our members attests to the benefits, and indeed, the necessity of use of Midodrine HCl in patients who demonstrate refractoriness to other treatment strategies for symptomatic hypotension.

For the reasons enumerated above, the ASN strongly urges the FDA to take the chronic hemodialysis population into consideration when deciding the future of Midodrine HCl. This drug improves the quality of life for numerous patients suffering from many diseases, including refractory symptomatic intradialytic hypotension. As the FDA decides on a final course of action, we respectfully urge FDA to keep this drug available indefinitely to those patients for whom it is a medical necessity.

Thank you for your time and consideration. To discuss ASN's comments, please contact ASN Director of Policy and Public Affairs, Paul C. Smedberg, at (202) 416-0640 or at psmedberg@asn-online.org.

Sincerely,



Sharon Anderson, MD, FASN
President

cc: Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

Norman Stockbridge, MD, Ph.D.

Director

Division of Cardiovascular and Renal Products