



To be as brave as the people we help.

***An Open Letter from Shire to Patients
Prescribed ProAmatine® (midodrine HCl)***

At Shire, nothing is more important to us than helping patients by providing medicines and treatments in a way that is ethical, transparent and compliant with regulations that guide our industry. In that spirit, we provide this update to patients and their families whose lives have been helped through the use of ProAmatine® (midodrine HCl), a Shire medicine approved in the United States under an accelerated approval process for the treatment of symptomatic orthostatic hypotension (SOH).

ProAmatine in its five generic forms of midodrine remains available to patients today.

This is a unique situation for all involved and we at Shire are doing everything we can to keep this medicine on the market so patients can continue to access it.

As the New Drug Application (NDA) holder for ProAmatine, Shire remains committed to ensuring midodrine remains available for patients who critically need this medicine and who would be left without alternative treatments should it be withdrawn from the market. Without marketing authorization approval from the U.S. Food and Drug Administration (FDA) for the ProAmatine NDA, the generic versions of ProAmatine – midodrine – would no longer be available to patients.

Shire continues to work closely with FDA in the hopes of either securing final FDA approval of this medicine based on the data submitted following two post-marketing clinical trials, or establishing an agreed development plan for conducting additional clinical trials. While we at Shire continue to work with the FDA to design trials that further confirm the clinical efficacy of ProAmatine, we've reached an impasse and we now believe the fastest way to get the final approval for this medicine is to present our data at a public hearing, thereby sparing patients the additional hardships of clinical trials.

Shire has no financial interest in midodrine; Shire no longer manufactures, distributes or markets ProAmatine. Beginning in 2003 and continuing to today, midodrine has been manufactured and distributed by generic pharmaceutical companies. As the NDA holder, Shire has continued to invest in the needed processes to ensure this medicine remains available for patients and their families who rely on it, and Shire has worked diligently with FDA to develop a path forward that would allow the NDA to maintain its marketing authorization thus allowing the generic versions of ProAmatine to remain available for patients.

ProAmatine was approved in 1996 under Subpart H (an accelerated approval process) for the treatment of SOH, with a post-approval commitment to conduct two clinical trials to verify the clinical effect of midodrine. The initial approval was based on ProAmatine's demonstrated ability to significantly raise blood pressure in patients with SOH. In 2000, Shire acquired ProAmatine and completed two clinical post-marketing trials as required and submitted the results to FDA in 2005. FDA took the position that these trials were

inconclusive and requested that additional trials be completed. Shire disagrees with the FDA and believes that these trials, together with 15 years of clinical experience, have established the clinical efficacy of ProAmatine and provide the necessary data to support the full approval of ProAmatine.

From all of us at Shire, thank you for your continued interest, support and understanding.

If you have questions or would like additional information, please contact us at 800-828-2088, or send an email to our Customer Service team at CustomerService@shire.com

Important Safety Information

Warning: Because ProAmatine® can cause marked elevation of supine blood pressure, it should be used in patients whose lives are considerably impaired despite standard clinical care. The indication for use of ProAmatine® in the treatment of symptomatic orthostatic hypotension is based primarily on a change in a surrogate marker of effectiveness, an increase in systolic blood pressure measured one minute after standing, a surrogate marker considered likely to correspond to a clinical benefit. At present, however, clinical benefits of ProAmatine®, principally improved ability to carry out activities of daily living, have not been verified.

CONTRAINDICATIONS

ProAmatine® is contraindicated in patients with severe organic heart disease, acute renal disease, urinary retention, pheochromocytoma or thyrotoxicosis. **ProAmatine®** should not be used in patients with persistent and excessive supine hypertension.

Please see ProAmatine's [Full Prescribing Information](#).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

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