Eli Lilly and Company
Lilly Corporate Center
Indianapolis, Indiana 46285
U.S.A.

December 15, 2003

IMPORTANT DRUG WARNING – New Prescribing Information

Dear Health Care Professional,

This letter is to advise you of the possibility of patients falling asleep while performing daily activities, including operation of motor vehicles, while receiving treatment with Permax® (pergolide mesylate), a dopamine agonist, indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease. While somnolence is a common occurrence in patients receiving Permax and many clinical experts believe that falling asleep while engaged in activities of daily living only occurs in the context of pre-existing somnolence, many patients who have fallen asleep have perceived no warning. Health Care Professionals should be alerted to the potentially serious risks associated with the events and should carefully evaluate their patients for the presence of somnolence, and should have a discussion with them.

To communicate this important safety information, the Warnings section in the US Package Insert for Permax has been updated to include the following:

> ***Falling Asleep During Activities of Daily Living* — Patients treated with Permax have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles which sometimes resulted in accidents. Although many of these patients reported somnolence while on Permax, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events had been reported as late as 1 year after the initiation of treatment.**
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> **Somnolence is a common occurrence in patients receiving Permax. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.**
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> **Before initiating treatment with Permax, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with Permax such as concomitant sedating medications or the presence of sleep disorders. If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require participation (e.g., conversations, eating, etc.), Permax should ordinarily be discontinued. If a decision is made to continue Permax, patients should be advised to not drive and to avoid other potentially dangerous activities.**
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> **While dose reduction may reduce the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.**

The somnolence statement in the Information for Patients subsection of the Precautions section in the US Package Insert for Permax has been updated to include the following (new wording underlined):

> Because pergolide mesylate may cause somnolence and the possibility of falling asleep during activities of daily living, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that pergolide mesylate therapy does not affect them adversely. Patients should be advised that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not

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drive or participate in potentially dangerous activities until they have contacted their physician. Due to the possible additive sedative effects, caution should also be used when patients are taking other CNS depressants in combination with pergolide mesylate.

Our primary concern is the safety and well–being of patients who use Permax. If you become aware of any case(s) of the event described above in patients treated with Permax or other dopaminergic agents, please report the event promptly. You may contact Amarin Pharmaceuticals, Inc., our US licensee for Permax, regarding events associated with Permax at 1-800-969-4877, or you may contact the FDA MedWatch program by phone at 1-800-FDA-1088, by fax at 1-800-FDA-0178, or by mail to MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

If you have any additional questions regarding Permax, you may contact Amarin Pharmaceuticals, Inc. at 1-800-969-4877.

Sincerely,

Patrizia A. Cavazzoni, MD
Director, Global Product Safety – Neuroscience
Eli Lilly and Company

Permax is a registered trademark of Eli Lilly and Company, and is licensed exclusively in the United States to Amarin Pharmaceuticals, Inc. Please see accompanying Prescribing Information.