CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-514

SUMMARY REVIEW

MEMORANDUM

DATE: March 18, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22514

SUBJECT: Action Memo for NDA 22514, for the use of Mirapex ER (pramipexole dihydrochloride) Extended Release Tablets for the treatment of the signs and symptoms of advanced idiopathic Parkinson's Disease (PD)

NDA 22514, for the use of Mirapex ER (pramipexole dihydrochloride) Extended Release Tablets for the treatment of the signs and symptoms of advanced idiopathic Parkinson's Disease (PD), was submitted by Boehringer Ingelheim Pharmaceuticals, Inc., on 5/20/09. Mirapex immediate release tablets have been marketed for the treatment of PD for several years (approved 7/1/97) and for Restless Legs Syndrome (11/7/06). Mirapex ER tablets were recently approved for the treatment of patients with early PD (2/19/10), based on the results of an 18 week assessment in a randomized, placebo controlled study in these patients.

This application contains a report of a single randomized controlled trial in patients with advanced PD. In addition, the application contains the results of a 33 week evaluation (continuation) of the study in early PD patients for which the week 18 results served as the basis for the recent approval in these patients described above. The application also contains safety data from both studies as well as from several other studies.

The application has been reviewed by Dr. Kenneth Bergmann, medical officer, Dr. Julia Luan, statistician, Dr. Antoine El-Hage, Division of Scientific Investigations, and Dr. David Podskalny, neurology team leader. The clinical team recommends that the application be approved.

I agree. As described in detail by Drs. Bergmann, Luan, and Podskalny, the multi-center, randomized, placebo and active controlled (Mirapex IR) study, performed entirely outside the United States, clearly showed significant effects for Mirapex ER compared to placebo on the primary outcome (Mean Change from Baseline on Parts II and III of the Unified Parkinson's Disease Rating Scale [UPDRS]) and on the key secondary outcome (Off Time while awake), as well as on several other secondary outcomes. The primary outcome was assessed at Week 18, but results at Week 33 were essentially the same. There were few numerical differences between the performance of the ER and IR tablets, although there were some outcomes for which the IR tablets-placebo contrasts reached nominal significance when the ER-placebo contrasts did not (e.g., Off Time at Week 33; Patient Global Rating).

As noted above, the application also contains the Week 33 results of the study in patients with early PD. These results mirror the results in this study seen at Week 18.

Examination of the safety data revealed no events not previously known to occur with this product. Worthy of note, however, is that this was the first development program to formally assess the occurrence of impulsive behaviors, long considered complications of dopaminergic therapy.

Specifically, the sponsor performed the modified Minnesota Impulsive Disorders Interview (MIDI) in these studies. This instrument assesses compulsive sexual behavior, buying, and gambling, and was performed at baseline and at various times during the studies. These data show that 6%, 3%, and 1% of patients with advanced PD treated with Mirapex ER, IR, and placebo, respectively, had confirmed positive responses on the MIDI.

There were no significant problems found at the three centers that were inspected, one in the Philippines, and two is Spain.

The sponsor has submitted substantial evidence of effectiveness for Mirapex ER in the treatment of patients with advanced PD, and there are no safety concerns that would preclude approval. Because Mirapex ER has been shown to be effective in both early and advanced PD, I will issue the attached approval letter, including product labeling with the following indication: “Mirapex ER tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson’s Disease”, without qualification related to stage of the disease. The sponsor and we have agreed to this label.

Russell Katz, M.D.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22514	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	TBD (PRAMIPEXOLE DIHYDROCHLORIDE)ER TABS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
03/19/2010