

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
201152Orig1s000

SUMMARY REVIEW

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 23, 2011

FROM: Jeffrey S. Murray M.D., M.P.H.
Deputy Director
Division of Antiviral Products

SUBJECT: Memorandum for NDA 201-152
Viramune XR (nevirapine) 400 mg Tablets

TO: Division files

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted an original NDA for Viramune XR, an extended release formulation of the previously approved Viramune IR tablets (first approved 1996). An oral solution of Viramune is also approved and marketed. The active ingredient of Viramune is nevirapine, a non-nucleoside HIV reverse transcriptase inhibitor. Viramune XR 400 mg tablets provide for once daily dosing, after a two-week lead-in period, whereas the previously approved products require twice daily dosing. All Viramune products require a two week lead in with half the daily dose given once daily. The lead-in period is reported to reduce the frequency of serious rash events during an initial period of auto-induction of drug metabolism.

Please refer to the primary clinical review written by medical officer Peter Miele, M.D., the cross discipline team leader memorandum written by Linda Lewis, M.D., and the statistical review written by Susan Zhou PhD and Lan Zeng Ph.D for detailed descriptions of study designs and efficacy and safety analyses.

Also refer to the microbiology review written by Lalji Mishra, PhD, and the clinical pharmacology review written by Vikram Arya Ph.D. Briefly, for details regarding virology and clinical pharmacology issues, respectively. Viramune XR Tablets 400 mg once daily yield lower AUC and C-trough levels than Viramune IR Tablets 200 mg twice daily, but mean trough levels exceed the calculated threshold for maintenance of HIV suppression throughout the dosing interval. Once daily dosing is more convenient than twice daily dosing and is expected to potentially increase adherence. Of note, drug-drug interactions are expected to be the same for NVP-XR as for the currently approved formulation; therefore, no new drug-drug interaction studies were submitted or were required with this NDA.

As noted in the Chemistry Review provided by Dr. Shrikant Pagay, "The sponsor has provided sufficient information on raw material controls, manufacturing

processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.” In addition all facilities have acceptable site recommendations.

This application is supported by data from two randomized, controlled, Phase 3 trials, one in treatment naïve patients and the other in patients on a stable HAART regimen that included Viramune IR. In both trials Viramune XR was compared to Viramune IR. The first trial (1100.1486) was considered pivotal and the second (1100.1526) was supportive. Trial 1100.1486 (VERxVE) was a randomized, double-blind, active controlled trial comparing the use of NVP-XR 400 mg once daily to NVP-IR 200 mg twice daily in combination with tenofovir DF/emtricitabine in treatment-naïve HIV-1 infected patients. In this trial the new formulation appeared to perform slightly better than the currently approved formulation. The proportion of patients with HIV-RNA levels less than 50 copies/mL at the 48 week time point was 80% for Viramune XR compared to 75% for Viramune IR, demonstrating clear noninferiority of the new formulation. In fact, the efficacy of the new formulation approached statistical significance for superiority. Likewise, the safety profile of the new formulation was similar to that of the prior formulation with slightly less rash and numerically fewer cases of serious rash. The slightly improved safety profile is plausible based on the pharmacokinetic profile.

The second trial, 1100.1526 (TRANxITION) was a randomized, open-label, clinical trial to investigate the efficacy and safety of switching HIV-1 infected subjects who were successfully treated with a NVP-IR based regimen to NVP-XR or keeping them on their NVP-IR (2:1 ratio). All subjects remained on their stable background antiretroviral drugs (abacavir/lamivudine, zidovudine/lamivudine, or tenofovir DF/emtricitabine) and randomization was stratified by background regimen. In this trial 94% of the participants remaining on Viramune IR and 96% of participants switching to Viramune XR had HIV-RNA levels less than 50 copies/mL at 24 weeks. Safety profiles were comparable.

Final Recommendation:

All of the reviewers and I concur that Viramune XR should be approved for the treatment of HIV for use in combination with other antiretrovirals. As suggested in clinical trial results, this new formulation may have a slightly better safety and efficacy profile than Viramune IR due to pharmacokinetics and more convenient administration. All Viramune dosing, however, must be commenced with a two week lead-in dose of Viramune IR 200 mg once daily for adults. Therefore both formulations are intended to remain on the market. Viramune oral solution is available for children unable to swallow tablets. Administration in children also requires a 2 week lead in with once daily dosing at half the recommended final daily dose.

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/s/

JEFFREY S MURRAY
03/24/2011