CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-145

SUMMARY REVIEW

Decisional Review for NDA 22-128

Date	October 12, 2007
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 22-145
Proprietary / Established (USAN) names	Isentress™/raltegravir
Dosage forms / strength	400 mg tablets
Proposed Indication(s)	For use in combination with other antiretroviral agents in treatment-experienced adult patients infected with multidrug resistant strains of HIV-1
Action	Approval

1. **Introduction to Review:** This Division Director's memorandum summarizes salient features of NDA 22-145, Merck Research Laboratories' (Merck) New Drug Application (NDA) for raltegravir, a new molecular entity that inhibits integration of viral DNA into host genomic material. This review will cover safety and efficacy in detail; brief comments will cover pharmacology/toxicology, clinical pharmacology and clinical microbiology.

2. **Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status:** Currently, there are almost 25 marketed antiretroviral products for HIV treatment. They fall into four distinct categories including nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and entry inhibitors, including the recently approved CCR5 antagonist category. As there are an estimated 40,000 new cases of HIV per year in the United States and tens of millions infected worldwide with the virus, there continues to be a need for novel drugs to overcome significant treatment issues related to drug resistance, toxicity and adherence.

   Raltegravir is an integrase inhibitor developed by Merck. This drug's unique mechanism of action involves inhibition of strand transfer between host and viral DNA. It has potent in vitro activity and is also active against multi-drug resistant HIV and dual /mixed tropic virus.

   This NDA was submitted in April, 2007 and received a priority review because it meets an unmet medical need. This application was also presented at the Antiviral Products Advisory Committee on September 5, 2007. The advisory committee unanimously recommended approval following data review presented by the applicant and DAVP staff.

3. **CMC:** All CMC issues have been adequately addressed. Please see CMC reviews by Drs. George Lunn and Ted Chang.

4. **Nonclinical Pharmacology/Toxicology:** A thorough pharmacology/toxicology review was performed by Dr.Ita Yuen. Per Dr. Yuen's review, pertinent findings in animal studies included the following: 1) raltegravir causes mucosal irritation; rodents appear to be more sensitive than dogs and rabbits, 2) mucosal irritation manifested as gastrointestinal bloating with glandular mucosal erosion in the stomach resulted in deaths at doses $\geq$ 500 mg/kg/day or three-fold above the to-be-marketed dose of 400 mg BID, 3) raltegravir is neither genotoxic nor mutagenic, 4) the carcinogenic potential is being evaluated in ongoing two-year carcinogenicity studies in rats and mice; histologic examination of animals in the ongoing carcinogenicity studies revealed squamous cell carcinomas of the nasopharynx and nose that were felt to be secondary to the local irritative properties of raltegravir, and 5) raltegravir readily crosses the blood-brain and blood-placental barriers and is secreted in the milk of animals.

5. **Clinical Pharmacology/Biopharmaceutics:**
Important points discerned by the clinical pharmacology review team include the following:

   - Metabolism is mediated through UGT1A1 and renal excretion is a minor pathway.

   - Raltegravir is a UGT1A1 and P-gp substrate. It is not an inhibitor of CYP3A4 nor is it an inducer.

   - Food effect is significant. Although a high fat meal slowed the rate and extent of absorption, phase 2 and 3 trials were conducted with raltegravir dosing without regard to food. This issue was extensively discussed at the Antiviral Products Advisory Committee.

   - Dose-finding studies were adequate. It was determined that the dose of raltegravir should be 400 mg BID despite observed pharmacokinetic variability. Sources of variability include food, pH, UGT1A1 polymorphisms and drug interactions.

   - Per the review team's comments, the lack of a relationship between virologic success and Cmin may be due to the fact that exposures are within the asymptotic region of the Cmin-virologic success curve, within concentrations studied.

   - Raltegravir is unlikely to inhibit metabolism of co-administered drugs metabolized by CYP450 enzymes, UGT enzymes or P-gp.

- Raltegravir plasma concentrations were increased in the presence of atazanavir with or without ritonavir and decreased in the presence of tipranavir/ritonavir. The review team determined that raltegravir concentrations resulting in up to a 2-fold increase in AUC for safety and a 60% decrease in trough concentrations were not clinically relevant based on data from phase 2 and 3 trials.

- The package insert will contain precautionary wording to address concomitant use of rifampin, a strong inducer of UGT1A1; other inducers such as efavirenz, nevirapine, rifabutin and St. John's wort may be used with the recommended dose of raltegravir.

6. **Clinical Microbiology**: Please see extensive review by Dr. Sung Rhee. Paired sequence analysis of baseline and on-treatment samples were examined for genotypic mutations. Treatment samples from 77 subjects with evidence of virologic failure revealed 97% with genotypic mutations in the HIV-1 integrase coding region. Three key mutations were identified: Y143C/H/R, Q148H/K/R and N155H. Each of these key mutations was usually accompanied by $\geq$ 1 additional mutation.

7. **Clinical Efficacy/Statistical:** Please see reviews by Drs. Sarah Connelly and Karen Qi. Efficacy and safety were based primarily on phase 2, 004 (treatment-naïve) and 005 (treatment-experienced) and phase 3 studies 018 and 019, identically designed trials that were implemented in different geographic regions. Briefly, raltegravir was shown to be safe and effective in phase 2/3 trials. Data reviewed from phase 2 studies allowed FDA to determine that the drug was highly potent such that the applicant submitted their marketing application with 100% of week 16 data and only 60% of week 24 results. The applicant submitted 100% of week 24 safety data during the review of the NDA. This approach does not reflect a change in policy with regard to the amount of data that is required for a marketing application, but rather it was an exception for a potent product within a new class of antiretrovirals.

   More specifically, both 018 and 019 were randomized, double-blind, placebo-controlled phase 3 trials that compared raltegravir 400 mg BID plus an optimized background to an optimized background alone in triple-class resistant HIV-1 infected subjects. The primary efficacy endpoint was HIV RNA < 400 copies/ml at week 16; key secondary endpoints included proportion of subjects with HIV RNA < 50 copies/ml and change from baseline in CD4 count. Subjects exhibiting virologic failure after week 16 were eligible to enter an open-label raltegravir arm. Analyses were pooled as the trials were identically designed.

Over 1000 patients were screened for Studies 018 and 019 and 703 were randomized in the two trials to receive raltegravir plus OBT or OBT alone. This was an advanced population with more than 90% of subjects with a diagnosis of AIDS. Median number of antiretroviral agents was 12. Approximately 60% had a GSS of 0-1 and approximately half of randomized subjects had a PSS of 0-1.

Results were highly statistically significant for the integrated analysis of efficacy as determined by the primary endpoint, HIV RNA < 400 copies/ml at week 16 comparing raltegravir plus OBT compared to OBT alone, 77% versus 42% respectively; durability of effect was seen at week 24 with 76% of raltegravir subjects achieving the primary endpoint compared to 39% on OBT alone. Regarding the secondary endpoint of < 50 copies of HIV RNA, 63% versus 33% met this endpoint with a p-value < 0.001. Change from baseline in CD4 count was also highly statistically significant with subjects receiving raltegravir experiencing a change from baseline in CD4 count of 89 cells/mm3 compared to 35 cells/mm3 for OBT alone at week 24.

Subjects with a PSS/GSS of 0 had a response rate of 41% compared to 4-5% , raltegravir plus OBT compared to OBT alone for the endpoint of HIV RNA < 50 copies /ml. Meaningful differences were also seen with PSS/GSS of 1-2. As the PSS/GSS increased to 3 or more, little difference was seen between treatment arms. This is to be expected as there were more active drugs in the constructed regimens. Consistent treatment effects favored raltegravir regardless of race or gender, though numbers of females and non-Caucasians were more limited as compared to males and Caucasians. To address this issue, the applicant has agreed to a post-marketing commitment to further examine the safety of raltegravir in underrepresented populations.

8. Safety: A total of 902 HIV infected subjects received at least one dose of raltegravir during the phase 2/3 studies at the time of the safety update report. The most commonly reported adverse reactions of all intensities and regardless of causality occurring in the adult treatment-experienced population in studies 005, 018 and 019 were diarrhea (16.6% versus 19.5%, raltegravir 400 mg BID plus OBT compared to OBT), nausea (9.9% versus 14.2 %), headache (9.7% versus 11.7%) and pyrexia (4.9% versus 10.3%).

Dr. Connelly also examined serious adverse events, overall and by causality in her review. Clinical adverse events occurring more frequently in raltegravir arms were fatigue (7.9% versus 4.6%), nasopharyngitis (6.1% versus 3.9%), rash (5.3% versus 2.5%) and herpes zoster (4.1% versus 0.7%). The majority of rash events were mild-to-moderate and no study discontinuations were reported in the phase 2/3 trials. Upon further analysis of events related to herpes zoster, approximately one-third of subjects had a prior history of herpes zoster.

No clear increase in malignancies was observed in the raltegravir database. An initial imbalance was seen between raltegravir and placebo arms. However, upon submission of additional data, the imbalance diminished as more cases were seen in placebo-treated subjects.

No dose-response relationship was observed with regard to hepatic events. In phase 2/3 trials there were 19% versus 14% hepatic events, raltegravir plus OBT versus OBT. There were seven hepatic SAEs in 5 subjects occurring in phase 3 trials; all were determined to be unrelated to use of raltegravir. The database was further examined for Hy's Law cases defined as AST and/or ALT $\geq$ 3x ULN, total bilirubin $\geq$ 2x ULN, no evidence of obstruction and no confounding conditions. Based on this definition, there were no Hy's Law cases. Subjects co-infected with hepatitis B and/or C had elevated rates of AST and ALT regardless of treatment group compared to subjects who were not co-infected.

Elevations of CK were noted in the database. An increase in CK was observed in approximately 6.6% of subjects receiving raltegravir compared to 4.1% in controls; association with clinical symptoms was balanced between the two groups. A minority of raltegravir-treated subject briefly interrupted study therapy due to elevated CK levels, but the temporal correlation with confounding factors makes it difficult to attribute causality to raltegravir use. A total of 3 cases of rhabdomyolysis and 2 cases of myopathy were reported in the phase 3 and expanded access programs. One subject appeared to have a positive rechallenge with elevated CK levels after restarting their raltegravir-based regimen; however, the subject was asymptomatic and CK values normalized without interrupting study therapy. The Applicant has agreed to include CK laboratory data, rhabdomyolysis and myopathy in the PI, and longer term data and safety monitoring will be collected to allow further characterization of any potential relationship between raltegravir, elevated CK levels and clinical adverse events.

9. Mortality: There were 16 deaths in studies 005, 018 and 019 through the safety update report (frozen file lock as of 2/16/07); there were no deaths in the treatment naïve study 004. Causes of death were consistent with an advanced population and there was no specific clustering of causes, although the majority were related to infection. Death rates irrespective of time on or off study drug were approximately 2.2% for the raltegravir arms compared to 1.1% on placebo. Subjects who died were more advanced in their disease at baseline compared to subjects who didn't die. Week 24 mortality rates per 100 patient-years were 2.8 for raltegravir-treated subjects compared to 2.5 for others. This is similar to other recent drug development programs for a highly treatment-experienced HIV-infected population.

10. Risk Minimization Considerations: The applicant has agreed to post-marketing commitments to examine long-term effects of raltegravir. Data up to 5 years will be submitted for studies 018 and 019. In addition Merck has agreed to conduct a separate observational study also for 5 years to examine serious medical conditions.

Conclusions and Recommendations: I am in agreement with the Raltegravir Review Team that raltegravir should be approved under the accelerated approval regulations based on the totality of the data contained in NDA 22-145. It has been demonstrated that the benefits of using raltegravir in the indicated population exceed the risks of using raltegravir. Labeling and post-marketing commitments address the concerns of the Antiviral Products Advisory Committee. With the approval of a new drug class, we can construct highly active treatment regimens for advanced patients with multidrug resistant HIV-1.

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

/s/

Debra Birnkrant
10/12/2007 10:34:57 AM
MEDICAL OFFICER

final DD memo for raltegravir

Edward Cox
10/12/2007 12:18:15 PM
MEDICAL OFFICER