

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-145**

**OFFICE DIRECTOR MEMO**

## Office Director Memo

**Applicant:** Merck & Co., Inc.

**NDA #:** 22-145

**Established Name:** raltegravir

**Trade Name:** Isentress

### Proposed Indication and Usage Section

#### INDICATIONS AND USAGE

ISENTRESS in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

This indication is based on analyses of plasma HIV-1 RNA levels up through 24 weeks in two controlled studies of ISENTRESS. These studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, NRTI, PI) treatment-experienced adults.

The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response [see Clinical Studies (14)].

The safety and efficacy of ISENTRESS have not been established in treatment-naïve adult patients or pediatric patients.

There are no study results demonstrating the effect of ISENTRESS on clinical progression of HIV-1 infection.

**Proposed Dose:** For the treatment of patients with HIV-1 infection, the dosage of ISENTRESS is 400 mg administered orally, twice daily with or without food.

**Date of Initial Submission:** April 13, 2007

**PDUFA Goal Date:** October 13, 2007

**Regulatory Action:** Approval

#### Background

Isentress (raltegravir) is an HIV integrase inhibitor. It acts by inhibiting the integration of HIV DNA into the host cell genome. It is the first in a new class of HIV-1 antiviral drugs.

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of raltegravir for the treatment of HIV infection in antiretroviral experienced adult patients. For a detailed discussion of NDA 22-145, the reader is referred to the individual discipline specific reviews. In addition Dr. Marcus's Team Leader's Memo and Dr. Birnkrant's Division Director's Memo summarize key issues in the NDA submission. This memorandum will focus on selected issues from the application.

### **Chemistry Manufacturing and Controls**

The chemistry manufacturing and controls are summarized in the Chemists' review which recommends approval from the standpoint of CMC for Isentress (raltegravir 400 mg tablet). Facilities inspections were performed and found to be acceptable. The recommendation regarding CMC is for approval.

### **Pharmacology Toxicology**

The recommendation from Dr. Yuen with regards to the pharm/tox studies is for approval from a pharm/tox standpoint. In animal studies the drug was noted to cause mucosal irritation; the finding was related to dose and duration and rodents were more susceptible than dogs and rabbits. In genotoxicity assays, raltegravir was found to not to be mutagenic or clastogenic, with or without metabolic activation. The two-year carcinogenicity studies in rats in mice are ongoing at this time and are scheduled to continue through the fourth quarter of 2007. The results of the carcinogenicity studies should be available at the time of traditional approval. Raltegravir was found to readily cross the blood-brain and blood-placental barriers and it is secreted in animal milk. Isentress is categorized as Pregnancy Category C.

### **Microbiology**

The microbiologic assessment of raltegravir is discussed in Dr. Rhee's microbiologist's review. The microbiologist's recommendation is for approval. Isentress is an HIV integrase inhibitor that acts by inhibiting the enzyme that is involved in the integration of viral DNA into the host cell genome. The microbiology review includes analyses of mutations associated with resistance to raltegravir. The product label includes the mutations observed in the integrase coding sequence that contribute to raltegravir resistance.

### **Clinical Pharmacology**

The clinical pharmacology of raltegravir is discussed in the clinical pharmacology and biopharmaceutics and pharmacometrics reviews which note that the information provided by the applicant is acceptable. Raltegravir was noted to exhibit high pharmacokinetic variability. Raltegravir is approximately 83% bound to plasma proteins. Hepatic clearance via glucuronidation plays a major role in clearance of raltegravir; renal clearance of unchanged drug is a minor pathway. The glucuronidation of raltegravir is

mainly catalyzed by UGT1A1. Raltegravir is both a UGT1A1 and P-gp substrate. The label provides information on the drug-drug interactions to help guide healthcare providers prescribing raltegravir. No dose adjustment is recommended for patients with mild to moderate hepatic impairment or patients with renal insufficiency.

### **Clinical Efficacy and Safety**

The results of the clinical trials evaluating the safety and efficacy of raltegravir are discussed in detail in the Medical Officer's Review and the Statistical Review, and also in the reviews prepared by Dr. Marcus and Dr. Birnkrant. The statistical review concludes that raltegravir is superior to placebo and the Medical Officer, Team Leader and Division Director recommend accelerated approval for raltegravir. The reader is referred to their reviews for a detailed discussion of the safety and efficacy findings.

### **Efficacy**

Data evaluating the efficacy of raltegravir were derived from two dose finding phase 2 studies (one in treatment naïve and one in treatment experienced patients) and two phase 3 studies in treatment experienced patients. Data from the two phase 3 placebo controlled trials in treatment experienced patients compared raltegravir with optimized background therapy to optimized background therapy (OBT) alone and found raltegravir to be superior to OBT based upon suppression of HIV-1 viral load at the 16 week time point and supported by data from the 24-week time point for 60% of patients. Raltegravir treated patients also experienced a greater increase in CD4 cell counts than patients on OBT. In the case of raltegravir, a new class of antiretroviral agent, for an unmet medical need, with promising activity in the phase 2 studies, we relied upon data from the 16 week endpoint as the primary endpoint supported by data at 24 weeks for approximately 60% of patients. The statistical reviewer evaluated the robustness of the data by performing sensitivity analyses; the sensitivity analyses did not change the conclusion that raltegravir is superior to placebo. The statistical reviewer also evaluated mortality rates using per-year exposure and survival analysis and no significant difference in mortality was noted between raltegravir and placebo groups within the limit of the available follow-up and number of events.

### **Safety**

A total of 902 HIV infected subjects received at least one dose of raltegravir in phase 2 and 3 studies, of whom 692 received raltegravir 400 mg BID. Of these 692 subjects, 548 received the dose for at least 24 weeks. The most common adverse events were diarrhea, nausea, headache and pyrexia.

One issue raised during the review of raltegravir was an apparent imbalance in the rates of malignancy of raltegravir versus placebo. With evaluation of additional data the imbalance did not persist, calling into question the initial observation. As part of the postmarketing commitments, the applicant will conduct additional follow-up along with a longer term observational study to further evaluate long term safety including malignancy.

As noted above, overall mortality was analyzed and there were no significant differences in mortality between treatment arms. The mortality rates for patients receiving raltegravir were 2.2% vs. 1.1% for the optimized background therapy arm. Taking into consideration time on study drug, the mortality rates per 100 patient-years were 2.8 for raltegravir and 2.5 for OBR patients. These rates are similar to other recent trials in treatment experienced populations.

Elevations in creatinine kinase (CK) and associated clinical events were evaluated in the phase 2 and phase 3 database. For CK elevations of any grade, the rates for raltegravir treated patients were 13.9% compared to 9.4% for control patients. Limiting the analysis to grade 2 through 4 CK elevations found a rate of reporting of 6.6% in the raltegravir arm and 4.1% in the control arm. Additional analyses for the clinical event of myalgias, myositis, arthralgia, in association with CK elevations found few events in the database and given the limited number of events, rates for these events were not dissimilar across study arms. In the expanded access program 3 cases of rhabdomyolysis and 2 cases of myopathy have been reported. One subject appeared to have a positive rechallenge. The product labeling for raltegravir includes information in the Adverse Reactions section of the label on CK elevations and also notes that rhabdomyolysis and myopathy have been observed but that the relationship with raltegravir is not clear. Healthcare providers are advised to use raltegravir with caution in patients at increased risk for these conditions, such as patients who are also receiving other medications that are associated with rhabdomyolysis and myopathy.

Analysis of the phase 2 and 3 database limited to the double-blind treatment period found an imbalance in herpes zoster events between raltegravir 3.8% (29/755) vs. 1.9% (6/320). One third of these patients had a prior history of herpes zoster. herpes zoster among the listed Additional information will be obtained post accelerated approval on herpes zoster adverse reactions from additional data from ongoing clinical trials including the longer term follow-up of studies 018 and 019.

Rash events occurred in 7.2% vs. 5.3% of control patients. Most of the rash adverse reactions were of mild to moderate intensity and no patients discontinued raltegravir because of rash in the phase 2 or phase 3 studies. There were a total of 14 hypersensitivity adverse reactions in 10 subjects in the double-blind treatment phase of the phase 2 and 3 studies; these events occurred in 0.8% (6/755) of raltegravir treated subjects and 1.3% (4/320) in the control group. There were two hypersensitivity reactions that were serious adverse reactions in two patients receiving raltegravir. Their therapy was interrupted, but they were able to later resume therapy.

The product labeling adequately describes findings from the safety evaluation to date. Additional data from ongoing studies, postmarketing commitments, and postmarketing surveillance will provide additional data to further characterize the safety profile of raltegravir.

**DSI Inspections / DDMAC / DMETS / DSRCS consults**

DMETS and DDMAC have consulted on the proprietary name and do not object to the use of the proprietary name Isentress. Comments from DMETS, DDMAC, DSRCS and SEALD were considered in revising the proposed product labeling.



The Division of Scientific Investigations performed inspections of four sites and did not identify any significant observations that would compromise the integrity of the data.

Pediatric studies required under PREA for patients between 4 weeks and 18 years of age have been deferred as noted in the approval letter. This requirement was waived for patients less than 4 weeks of age.

**Advisory Committee**

The application was presented to the Antiviral Drugs Advisory Committee on September 5, 2007. The Committee voted unanimously that the safety and efficacy supported accelerated approval for treatment of treatment-experienced adult patients infected with multi-drug resistant strains of HIV-1.

**Risk Benefit Summary**

The overall risk and benefits for Isentress based upon the NDA database support the accelerated approval under Subpart H of Isentress for treatment of treatment experienced patients with ongoing viral replication and HIV-1 strains resistant to multiple anti-retroviral agents. Isentress is a new class of antiretroviral agent, an HIV integrase inhibitor that can be used as component of an active antiretroviral regimen in treatment experienced patients with resistance to other antiretroviral therapies and ongoing HIV viral replication. Raltegravir addresses an unmet medical need in the population of patients who need additional treatment options.

**Postmarketing Study Commitments**

The postmarketing study commitments including commitments for accelerated approval under Subpart H and Pediatric studies are enumerated in the action letter. There is also a postmarketing commitment to perform a study designed to get additional information on a more diverse patient population.

**Summary**

I concur with the assessment of the review team that adequate safety and efficacy information have been provided for Isentress (raltegravir) for the treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents under the subpart H accelerated approval regulations for serious or life-threatening illnesses (21CFR §314.510). The clinical studies show a clear effect on viral load and CD4 cell count and the safety profile based upon the available data is acceptable. The product labeling adequately describes the available information on Isentress. Approval under Subpart H is appropriate for Isentress given that it is a new class of antiretroviral agent and can be used to construct antiretroviral treatment regimens in treatment experienced patients with clinical isolates resistant to other classes of antiretroviral drugs. As part of approval under Subpart H, the applicant will study the drug further to verify and describe its clinical benefit as described in the postmarketing study commitments under Subpart H listed above.

**Appears This Way  
On Original**

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

/s/

-----  
Edward Cox  
10/12/2007 12:27:04 PM  
MEDICAL OFFICER