FDA Accepts Merck’s NDA for Fixed-Dose Combination of Raltegravir with Lamivudine

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If Approved, Fixed-Dose Combination Would Be Used with Other Antiretroviral Agents for the Treatment of HIV-1 in Adults, Adolescents and Certain Pediatric Patients

Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the New Drug Application (NDA) for a fixed-dose combination (FDC) of raltegravir with lamivudine for the treatment of HIV-1 infection (MK-0518B) has been accepted for standard review by the U.S. Food and Drug Administration (FDA). Merck is seeking FDA approval for 150 mg lamivudine/300 mg raltegravir, in combination with other antiretroviral (ARV) agents, for the treatment of HIV-1 in adults, adolescents (16 years of age and older) and pediatric patients (6 through 16 years of age and weighing at least 30 kg). Raltegravir is currently marketed as ISENTRESS® in the United States. Several different formulations of ISENTRESS are currently available, including a film-coated tablet (400 mg), chewable tablets (25 mg and 100 mg) and oral suspension (single use 100-mg packet). The MK-0518B FDC contains a new formulation of raltegravir.

“We are pleased that the FDA has accepted our application for a fixed-dose combination of raltegravir and lamivudine. This combination pairs two HIV medications and, if approved, will offer prescribers an additional option in the treatment regimens of HIV-1 patients,” said Dr. Nick Kartsonis, executive director, clinical research, Merck Research Laboratories. “This filing is another example of Merck's commitment to HIV.”

ISENTRESS (raltegravir) is indicated in combination with other ARV agents for the treatment of HIV-1 infection in patients 4 weeks of age and older. The use of other active agents with ISENTRESS is associated with a greater likelihood of treatment response.
Important Selected Safety Information

Severe, potentially life-threatening and fatal skin reactions have been reported. This includes cases of Stevens-Johnson syndrome, hypersensitivity reaction and toxic epidermal necrolysis. Immediately discontinue treatment with ISENTRESS and other suspect agents if severe hypersensitivity, severe rash, or rash with systemic symptoms or liver aminotransferase elevations develops and monitor clinical status, including liver aminotransferases closely.

Immune reconstitution syndrome can occur, including the occurrence of autoimmune disorders with variable time to onset, which may necessitate further evaluation and treatment.

ISENTRESS chewable tablets contain phenylalanine, a component of aspartame, which may be harmful to patients with phenylketonuria.

Coadministration of ISENTRESS with drugs that are strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 may result in reduced plasma concentrations of raltegravir. Coadministration of ISENTRESS with drugs that inhibit UGT1A1 may increase plasma levels of raltegravir. Coadministration of ISENTRESS and other drugs may alter the plasma concentration of raltegravir. The potential for drug-drug interactions must be considered prior to and during therapy. Coadministration or staggered administration of aluminum and/or magnesium hydroxide-containing antacids and ISENTRESS is not recommended. Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. Therefore, the dose of ISENTRESS for adults should be increased to 800 mg twice daily during coadministration with rifampin. There are no data to guide coadministration of ISENTRESS with rifampin in patients below 18 years of age.

The impact of other inducers of drug metabolizing enzymes, such as phenytoin and phenobarbital, on UGT1A1 is unknown.

In drug interaction studies, raltegravir did not have a clinically meaningful effect on the pharmacokinetics of the following: hormonal contraceptives, methadone, lamivudine, tenofovir, etravirine, and darunavir/ritonavir.

The most commonly reported (≥2%) drug-related clinical adverse reactions of moderate to severe intensity in treatment-naïve adult patients receiving ISENTRESS compared with efavirenz were insomnia (4% vs 4%), headache (4% vs 5%), nausea (3% vs 4%), fatigue (2% vs 3%), and dizziness (2% vs 6%) respectively. In treatment-experienced adult patients receiving ISENTRESS, the most commonly reported (≥2%) drug-related clinical adverse reactions of moderate to severe intensity and at a higher incidence compared with placebo was headache (2% vs <1%). In both studies, intensities were defined as: Moderate (discomfort enough to cause interference with usual activity); or 

2
Severe (incapacitating with inability to work or do usual activity). In treatment-experienced pediatric patients 4 weeks through 18 years of age receiving ISENTRESS, the frequency, type and severity of drug-related adverse reactions were comparable to those observed in adults.

Grade 2-4 creatine kinase laboratory abnormalities were observed in subjects treated with ISENTRESS (raltegravir). Myopathy and rhabdomyolysis have been reported. Use with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions and patients with a history of rhabdomyolysis, myopathy or increased serum creatine kinase.

Rash occurred more commonly in treatment-experienced subjects receiving regimens containing ISENTRESS + darunavir/ritonavir compared to subjects receiving ISENTRESS without darunavir/ritonavir or darunavir/ritonavir without ISENTRESS. However, rash that was considered drug related occurred at similar rates for all 3 groups. These rashes were mild to moderate in severity and did not limit therapy; there were no discontinuations due to rash.

ISENTRESS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no adequate and well-controlled studies in pregnant women. In addition, there have been no pharmacokinetic studies conducted in pregnant patients. To monitor maternal-fetal outcomes of pregnant patients exposed to ISENTRESS, an Antiretroviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

About ISENTRESS

ISENTRESS is Merck's integrase inhibitor for the treatment of HIV-1 infection in adult and pediatric patients ages four weeks and older and weighing at least 3 kg as part of combination HIV therapy. ISENTRESS works by inhibiting the insertion of HIV-1 DNA into human DNA by the integrase enzyme and has demonstrated rapid antiviral activity. Inhibiting integrase from performing this essential function limits the ability of the virus to replicate and infect new cells. ISENTRESS is now approved as part of combination therapy in more than 76 countries for use in treatment-naïve adult patients with HIV-1 and in more than 114 countries for use in treatment-experienced adult patients with HIV-1. ISENTRESS, in combination therapy, for use in children and adolescents with HIV-1 ages two years and older has also been approved for use in 35 countries, and ISENTRESS oral suspension for infants at least four weeks of age is approved for use in the United States. Merck is continuing to move forward with filings of ISENTRESS for oral suspension in additional countries around the world.

To assist patients taking ISENTRESS, Merck offers the SUPPORT™ program, which provides personal support and
patient advocacy regarding individual reimbursement issues. For more information about the SUPPORT™ program, please visit www.merckhelps.com or call 1-800-850-3430.

About Merck

Today's Merck is a global healthcare leader working to help the world be well. Merck is known as MSD outside the United States and Canada. Through our prescription medicines, vaccines, biologic therapies, and consumer care and animal health products, we work with customers and operate in more than 140 countries to deliver innovative health solutions. We also demonstrate our commitment to increasing access to healthcare through far-reaching policies, programs and partnerships. For more information, visit www.merck.com and connect with us on Twitter, Facebook and YouTube.

Forward-Looking Statement

This news release includes “forward-looking statements” within the meaning of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of Merck's management and are subject to significant risks and uncertainties. There can be no guarantees with respect to pipeline products that the products will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; Merck’s ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of Merck's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those
described in the forward-looking statements can be found in Merck's 2013 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC’s Internet site (www.sec.gov).

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