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# Merck Receives FDA Approval for ISENTRESS® (raltegravir), in Combination with Other Antiretroviral Agents, for the Treatment of HIV-1 Infection in Newborns Weighing at Least 2 kg

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## *Only Integrase Inhibitor Approved in the United States for Treatment of HIV-1 in Newborns from Birth to 4 Weeks of Age*

KENILWORTH, N.J. – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the U.S. Food and Drug Administration (FDA) has approved ISENTRESS® (raltegravir), the company's integrase inhibitor, for use in combination with other antiretroviral agents, for the treatment of HIV-1 in neonates – newborn patients from birth to four weeks of age – weighing at least 2 kg. The FDA approval for the use of ISENTRESS in the treatment of HIV-1 in neonates is supported by results from an open-label, multicenter clinical study, IMPAACT P1110, evaluating the safety and pharmacokinetics of ISENTRESS for oral suspension in 42 full-term HIV-1 exposed newborns at high risk for acquiring HIV-1 infection from their mothers.

“Because clinical research on the use of antiretroviral drugs to treat newborns with HIV-1 infection has been limited, few antiretroviral agents are approved for this population,” said Dr. Eliav Barr, senior vice president, global clinical development, infectious diseases and vaccines, Merck Research Laboratories. “With this FDA approval, ISENTRESS becomes the only integrase inhibitor approved in the U.S. for the treatment of HIV-1, in combination with other antiretroviral agents, for neonates weighing at least 2 kg. This achievement underscores Merck’s unwavering commitment to the development of treatment options for HIV-1.”

ISENTRESS does not cure HIV-1 infection or AIDS. 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. For more information, see “Selected Safety Information” below.

The use of ISENTRESS is not recommended in pre-term newborns or infants weighing less than 2 kg, as no data are available in these populations. If the mother has taken ISENTRESS or ISENTRESS HD within two to 24 hours before delivery, the newborn’s first dose should be given between 24 to 48 hours after birth.

## About IMPAACT P1110

The IMPAACT P1110 study used a two-cohort design. Cohort 1 newborns received two single doses of ISENTRESS for oral suspension: the first within 48 hours of birth and the second at seven to ten days of age. Cohort 2 newborns received daily dosing of ISENTRESS for oral suspension for six weeks at different weight-based doses. Sixteen newborns were enrolled in Cohort 1 (10 were exposed to ISENTRESS in utero and 6 were not) and 26 in Cohort 2 (all unexposed to ISENTRESS in utero); all infants received a standard of care antiretroviral drug regimen for prevention of mother to child transmission. All enrolled infants were followed for safety for 24 weeks. At the completion of the study, all patients were HIV-1 negative. The safety profile of ISENTRESS in this study was comparable to that observed in adults.

## Selected Safety Information about ISENTRESS (raltegravir)

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.

Co-administration of ISENTRESS with drugs that are strong inducers of uridine diphosphate glucuronosyltransferase (UGT) 1A1 may result in reduced plasma concentrations of raltegravir. Co-administration of ISENTRESS with drugs that inhibit UGT1A1 may increase plasma levels of raltegravir.

Co-administration 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. Co-administration or staggered administration of aluminum and/or magnesium-containing antacids and ISENTRESS is not recommended.

During co-administration with rifampin, the recommended dosage of ISENTRESS in adults is 800 mg twice daily. Rifampin, a strong inducer of UGT1A1, reduces plasma concentrations of ISENTRESS. There are no data to guide co-administration of ISENTRESS with rifampin in patients below 18 years of age.

The impact of other strong inducers of drug metabolizing enzymes on raltegravir is unknown (e.g., Carbamazepine, Phenobarbital, and Phenytoin). Co-administration of ISENTRESS with other strong inducers is not recommended.

### **About ISENTRESS (raltegravir)**

Approved in 2007, ISENTRESS was the first integrase inhibitor developed for the treatment of HIV-1 infection. ISENTRESS is one of the regimen options recommended by the U.S. Department of Health and Human Services – in combination with other antiretroviral agents – as a first-line therapy in treatment-naïve HIV-1 infected adults. ISENTRESS, in combination with other antiretroviral agents, is also approved to treat HIV-1 infection in pediatric patients weighing at least 2 kg.

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 approved as part of combination therapy in 112 countries for treatment of HIV-1 infection in adult patients and adolescents. ISENTRESS, in combination therapy, for use in children and adolescents with HIV-1 aged two years and older has been approved for use in 69 countries, and ISENTRESS for oral suspension for infants at least four weeks of age is approved for use in 33 countries. ISENTRESS for oral suspension is also now approved in the U.S. for the treatment of HIV-1 in newborns from birth to four weeks of age and weighing at least 2 kg.

### **Selected Safety Information about ISENTRESS (raltegravir) Continued**

The most commonly reported ( $\geq 2\%$ ) drug-related clinical adverse reactions of moderate to severe intensity in treatment-naïve adult patients receiving ISENTRESS compared with efavirenz were headache (4% vs 5%), insomnia (4% vs 4%), nausea (3% vs 4%), dizziness (2% vs 6%), and fatigue (2% vs 3%), respectively. In treatment-experienced adult patients receiving ISENTRESS, the most commonly reported ( $\geq 2\%$ ) 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 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. 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.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ISENTRESS during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Women infected with HIV-1 should be instructed not to breastfeed if they are receiving ISENTRESS due to the potential for HIV transmission.

### **About Merck**

For more than a century, Merck, a leading global biopharmaceutical company known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases. Through our prescription medicines, vaccines, biologic therapies 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 health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to advance the prevention and treatment of diseases that threaten people and communities around the world - including cancer, cardio-metabolic diseases, emerging animal diseases, Alzheimer's disease and infectious diseases including HIV and Ebola. For more information, visit [www.merck.com](http://www.merck.com) and connect with us on [Twitter](#), [Facebook](#), [Instagram](#), [YouTube](#) and [LinkedIn](#).

### **Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA**

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company'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; the company'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 the company's patents and other protections for innovative products; and the exposure to litigation, including patent

litigation, and/or regulatory actions.

The company 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 the company's 2016 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](http://www.sec.gov)).

Please see Prescribing Information for ISENTRESS (raltegravir) and ISENTRESS HD (raltegravir) at [http://www.merck.com/product/usa/pi\\_circulars/i/isentress/isentress\\_pi.pdf](http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf), Patient Information for ISENTRESS and ISENTRESS HD (raltegravir) at [http://www.merck.com/product/usa/pi\\_circulars/i/isentress/isentress\\_ppi.pdf](http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_ppi.pdf). The Instructions for Use also are available at [http://www.merck.com/product/usa/pi\\_circulars/i/isentress/isentress\\_ifu.pdf](http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_ifu.pdf)

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