アイセントレス錠600mg
に関する資料

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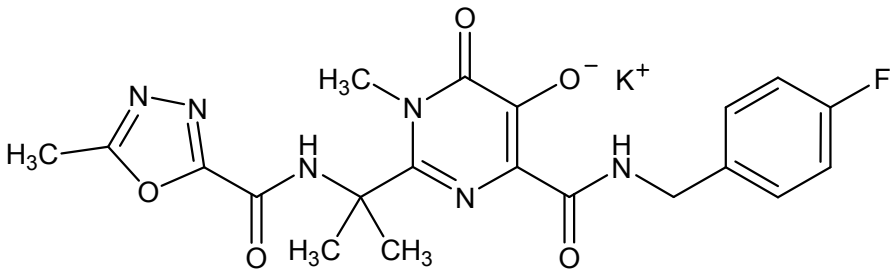
Raltegravir (USAN adopted name), also known as MK-0518, is a potent, HIV integrase strand transfer inhibitor active against the Human Immunodeficiency Virus (HIV-1) and represents the first in class HIV integrase inhibitor for the treatment of patients infected with the HIV. The chemical name for raltegravir potassium is *N*-[(4-Fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-4-pyrimidinecarboxamide monopotassium salt. Raltegravir is a white to off-white powder; it is soluble in water, slightly soluble in methanol, very slightly soluble in ethanol and acetonitrile and insoluble in isopropanol. The empirical formula is $C_{20}H_{20}FKN_6O_5$ and the molecular weight is 482.51. The structural formula is:



Raltegravir is currently indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in patients 4 weeks of age and older. As of 17-Mar-2016, raltegravir at a dose of 400 mg BID has received approvals in a total of 111 countries for the treatment of HIV-1 infection in adults and approximately 60 countries have extended the indication to include pediatric subjects weighing at least 25 kg. Raltegravir has not been withdrawn in any country.

Raltegravir twice daily formulations:

Raltegravir was approved in the United States in October 2007 and in the European Union in December 2007. The initial indication obtained in the marketing approvals was for the use of raltegravir at a dose of 400 mg BID in combination with other antiretroviral agents for the treatment of HIV 1 infection in treatment-experienced adult subjects with evidence of ongoing viral replication. In 2008, the 48 Week Treatment- Naïve Supplemental Application provided data on the safety and efficacy of raltegravir at a dose of 400 mg BID in combination with other antiretroviral therapy in HIV-infected treatment-naïve subjects to support broadening the indication to include treatment-naïve HIV infected adult subjects. On 08 July 2009, this Treatment-Naïve Application was approved by the Food and Drug Administration (FDA). On 23 July 2009 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion to recommend an extension to the indication to include antiretroviral therapy naïve adult subjects. In 2009, the 96 Week Treatment-Experienced and Treatment-Naïve Supplemental Application (referred to as the 96 Week Supplemental Application) provided additional long term data on the safety and efficacy of raltegravir in combination with other antiretroviral therapy in both HIV-infected treatment-

experienced and treatment-naïve adult subjects and these data were added to the raltegravir product information. In 2011, the 156 Week Treatment-Naïve Supplemental Application (referred to as the Naïve-3yr Supplemental Application) was submitted to provide long term data on the safety and efficacy of raltegravir in combination with other antiretroviral therapy in HIV infected treatment-naïve adult subjects and these data were added to the raltegravir product information. In 2012, the 240 Week Treatment-Naïve Supplemental Application (referred to as the Naïve-5yr Supplemental Application) was submitted to provide further long term data on the safety and efficacy of raltegravir in combination with other antiretroviral therapy in HIV infected treatment-naïve adult subjects and these data were added to the raltegravir product information.

Raltegravir is also available in two pediatric formulations, a chewable tablet formulation for BID dosing in 100 mg (scored) and 25 mg strengths, and granules for suspension for BID dosing (100 mg /sachet). Raltegravir was first approved for pediatric use in the United States in December 2011 and in the European Union on February 2013. The initial pediatric indication obtained in the marketing approvals, based upon data submitted in the first Pediatric Application (2 to 18 years), was for the use of raltegravir BID (as one of two formulations, the approved 400 mg tablet or a new chewable tablet formulation in 2 dosage strengths) in combination with other antiretroviral agents for the treatment of HIV 1 infection in children and adolescents 2 to 18 years of age. Raltegravir chewable tablets are available in dose strengths of 25 mg and 100 mg (scored) tablets. In December 2013 in the United States and in August 2014 in the European Union, the pediatric indication was extended to children 4 weeks to 2 years of age, based upon 48-week data submitted in the second Pediatric Application (4 weeks to 2 years) in infants and children receiving the raltegravir granules for oral suspension formulation.

Raltegravir once daily formulation:

There is a recognized need to simplify dosing of antiretroviral regimens in order to expand the options for the initial treatment of HIV-1 infection as well as increase patient compliance to maximize the probability of achieving and maintaining virologic suppression. The long term favorable safety and efficacy profile of raltegravir makes it a good option for the treatment of HIV-1 infection in treatment-naïve subjects. A once daily (QD) raltegravir dosing option would provide a more convenient treatment option for HIV-1 infected subjects.

Merck has developed a new 600 mg film coated tablet formulation for once daily use, as a 1200 mg dose (2x600 mg), which is currently in Phase 3 clinical evaluation (Protocol P292). P292 is a multicenter, double-blind (with in-house blinding), randomized, active-controlled study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of 1200 mg raltegravir q.d. (~533 subjects) compared with 400 mg raltegravir b.i.d. (~ 269 subjects) when each is given in combination with TRUVADA™ in HIV-1 positive, treatment-naïve adult subjects for treatment of HIV-1 infection. The study is now completely enrolled (N=802 patients) and the primary analysis (48 week) of the study has been completed.

The focus of this Supplemental Application is to submit 1) chemistry, manufacture, and control data for 600 mg film coated tablet; 2) clinical pharmacology and biopharmaceutics data of raltegravir 1200 mg once daily dosing with modeling and simulation results; 3) drug

interaction data of raltegravir once daily with agents that could affect raltegravir pharmacokinetics, and 4) safety and efficacy data to support the use of raltegravir 1200 mg (2x 600 mg) once daily for the treatment-naïve or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily.

ISENTRESS 1200 mg (2 x 600 mg) once daily has not been studied in pediatric patients. However, population PK modeling and simulation support the use of 1200 mg (2 x 600 mg) once daily in pediatric patients weighing at least 40 kg Therefore, the supplemental application includes the recommendation for the pediatric use of raltegravir 1200 mg once daily as "if weighing at least 40 kg, treatment-naïve or patients who are virologically suppressed on an initial regimen of ISENTRESS 400 mg twice daily". This recommended dose information is to be included in the Dosage and Administration Section of the ISENTRESS product circular. No change to the existing ISENTRESS indication is proposed in the application.