Translated from *Rev Prescrire* June 2014; 34 (368): 413

raltegravir

in HIV-infected children at least 2 years of age

NEW INDICATION

Only after prior treatment failure

● **The first integrase inhibitor to be approved for children; antiretroviral effect similar to that observed in adults in treatment failure; no first-line evaluation.**

POSSIBLY HELPFUL

The choice of antiretroviral therapy for HIV-infected children is largely extrapolated from experience in adults (1). First-line treatment consists of a combination of at least three antiretroviral drugs, including two nucleoside reverse transcriptase inhibitors and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor.

Since 2007, *raltegravir* (Isentress°, Merck Sharp Dohme), an integrase inhibitor, has been an additional option for adults in whom prior treatments have failed, despite a poorly documented long-term risk of autoimmune disorders and lymphoproliferative disease (2,3).

Raltegravir is now also authorised for HIV-infected children aged at least 2 years. Lower-dose, chewable tablets are also available in the European Union. How does *raltegravir* compare to other antiretrovirals when included in an optimised antiretroviral regimen for children?

raltegravir film-coated tablets and chewable tablets

ISENTRESS°

- **400 mg** of *raltegravir* per film-coated tablet

New dose forms and strengths

- **25 mg** of *raltegravir* per chewable tablet
- **100 mg** of *raltegravir* per chewable tablet (divisible)

antiretroviral; HIV integrase inhibitor

■ **New indication:** *"(…) in combination with other antiretroviral medicinal products for the treatment of human-immunodeficiency-virus (HIV-1) infection in (…) adolescents, and children from the age of two years".*

[EU marketing authorisation; centralised procedure]

No trials of first-line treatment. Clinical evaluation of *raltegravir* includes no trials of first-line therapy in children. It is based on a non-comparative trial in 126 children 2 years of age and older with high viral load despite antiretroviral therapy (4,5). Two-thirds of children had already received at least three classes of antiretroviral drugs. 96 children were treated with *raltegravir* at the approved dosage, adjusted for age and weight, sometimes using chewable tablets, in addition to an optimised antiretroviral regimen. After 48 weeks of treatment, the decline in viral load and the increase in the CD4+ T cell count were comparable to those observed in adults (4). *Raltegravir* resistance occurred in one-third of patients (4).

Skin reactions and psychological disorders should be monitored. The adverse effect profile in this small trial was similar to that observed in adults, mainly consisting of infections, digestive disorders, cutaneous reactions, fever, and neurological, psychiatric and musculoskeletal disorders (4,5). A case of severe allergic dermatitis was attributed to *raltegravir*. Suicidal behaviour was reported in two children, as well as a case of psychomotor hyperactivity, but trial investigators did not attribute these events to *raltegravir*. No cases of cancer or autoimmune disorders were reported, but follow-up was short (4,5).

Global pharmacovigilance data collected between 2007 and 2013, mainly in adults, show no particular cause for concern (6).

No bioequivalence between the two types of tablets. The film-coated tablets and chewable tablets are not bioequivalent (7). The flavouring and sweeteners added to the chewable tablets are intended to mask the bitter taste of *raltegravir*. Only the 100-mg tablets are divisible.

In practice. *Raltegravir* may be a useful addition to optimised antiretroviral treatment for HIV-infected adults and also children in treatment failure.

Selected references from Prescrire's literature search.

In response to our request for information, MSD provided us with minimal administrative documents.

1- Prescrire Editorial Staff "First-line antiretroviral treatment of HIV-infected children. A choice largely based on adult data" *Prescrire Int* 2011; **20** (115): 101-104.
2- Prescrire Rédaction "raltégravir-Isentress°. Multirésistances au HIV: une alternative à enfuvirtide + darunavir" *Rev Prescrire* 2008; 28 (294): 249-251.
3- Prescrire Editorial Staff "First-line raltegravir. No evidence of comparative effectiveness" *Prescrire Int* 2010; **19** (110): 248-250.
4- EMA - CHMP "Assessment report for Isentress. EMEA/H/C/860/X/24/G" 13 December 2012: 45 pages.
5- US FDA - CDER "Application Number: 203045Orig1s000-Medical Review(s)" 21 November 2011: 67 pages.
6- US FDA - CDER - Office of Surveillance and Epidemiology "Pediatric Postmarket Pharmacovigilance and Drug Utilization Review - Isentress (raltegravir)" 17 June 2013: 33 pages.
7- European Commission "SPC-Isentress" 17 December 2013: 69 pages.