



RALTEGRAVIR (RAL)

GENERAL INFORMATION

- Therapeutic class: Integrase inhibitor.
- WHO guidelines: Listed in the WHO guideline as potential third-line drug.⁶
- Indication: Indicated for treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.²²²
- Originator company and product brand name: Merck, Isentress.
- First approval by U.S. Food and Drug Administration (FDA): October 2007.²³
- WHO Model List of Essential Medicines (EML): Not included in the 17th edition.²⁴
- World sales of originator product: 2010: US\$ 1.09 billion; 2009: \$752 million; 2008: \$361 million; 2007: \$41 million.^{223, 224, 225}
- Patents: The basic patent was applied for in October 2002 by the Institute for Research in Molecular Biology (IRBM), Pomezia, Italy, one of Merck's research sites.²²⁶ The patent is due to expire in 2022. In 2005, Merck and IRBM applied for another patent on the potassium salt of RAL which can run up to 2025.²²⁷

PRICE INFORMATION

Developing country prices in US\$ per patient per year, as quoted by companies.

The price in brackets corresponds to the price of one tablet.

	Daily dose	Merck
Who can access this price?		See annex 2 & annex 10*
RAL 400mg tablet	2	675 (0.925)

*For the first time this year, Merck decided not to give standardised price discounts to Category 2 countries. See 'Spotlight on access issues' below.

SPOTLIGHT ON ACCESS ISSUES

Raltegravir (RAL) is the first of a new class of drugs integrase inhibitors, which has a novel mechanism of action and no apparent cross-resistance with other ARVs. This new drug option will be very important for patients who are treatment-experienced and may already be resistant to multiple antiretroviral agents.

RAL, unlike most drugs from the protease inhibitors class, does not require boosting with ritonavir (RTV).

In 2010, WHO released new recommendations which for the first time call for the need of third-line therapy. Many studies are ongoing – drugs likely to have anti-HIV activity in third-line regimens are RAL, etravirine (ETV), and boosted darunavir (DRV).⁷

Price remains an issue. The lowest price offered by Merck for some countries (see annex 10) is extremely high and unaffordable for developing countries. In 2011, Merck ceased offering standardised price discounts to all lower middle- and upper middle-income countries according to the World Bank Classification (see annex 6 for a list of these countries). The company proposes instead to negotiate discounted prices on a case-by case basis, based on country income and disease burden. This is concerning for the affordability of products in middle-income countries, especially given the extremely high prices charged in wealthy countries, at \$8,000.²²⁸

There is no generic raltegravir available.

Patents

Merck and IRBM applied for international patent applications^{229, 230, 231} under the Patent Cooperation Treaty (PCT) that facilitated the filing of these patent applications in many PCT member states, including some developing countries with generic drug manufacturing capacity, like Brazil, China, India and South Africa. IRBM was granted a patent in India in December 2007 which will not expire until 2022.²³² In India, an application on potassium salt of RAL²³³ is also pending review before the Indian patent office and warrants a pre-grant opposition. If granted, Merck's monopoly in India will be extended by an additional five years to 2027.

In Brazil, the Ministry of Health has announced that it is working on a technology transfer agreement with Merck for RAL.²³⁴ In 2010, the Brazilian government was paying \$5,870 ppy, a price that is expected to decrease with the technology transfer to \$4,000 in 2015.²³⁵ This approach – which is unlikely to ensure that prices are reduced to a level that is possible through unrestricted generic competition – may well establish a precedent for accessing other newer medicines in the future, both in Brazil and beyond.

As Brazil has one of the oldest HIV patient cohorts in developing countries, the need to access newer HIV medications is occurring earlier than in many other countries. The

access challenges Brazil experiences today will be faced by other developing countries in coming years, and Brazil's actions to improve the accessibility and affordability of RAL and other newer medications will have wider implications for all developing countries. Price reductions achieved by Brazil will set a target price for other countries, especially for other middle- and lower middle-income countries.

The size of Brazil's cohort is also critical. With approximately 4,450 people taking RAL, the country is one of the largest developing country consumers of the medicine,⁸² and could thus stimulate an international generic market where prices are reduced through competition and economies of scale.

In India, Merck is charging \$2,500 ppy.²³⁶

Paediatrics

The safety and efficacy of RAL in patients under 16 years of age have not been established.²³⁷

Paediatric studies are ongoing in children from four weeks old.²³⁸ As few treatment options exist for children with HIV, it is critical that paediatric studies of RAL be completed and adapted formulations be made available.