RITONAVIR (r or RTV)

GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO guidelines: Indicated for second-line as a booster, for adults, adolescents and children.[6, 22]
- Originator company and product brand name: Abbott, Norvir.
- First approval by U.S. Food and Drug Administration (FDA): March 1996 for the oral solution and June 1999 for capsules.[23]
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.[24]
- World sales of originator product: 2004: US$ 194 million; 2003: $93 million; 2002: $122 million.[256] After 2004, there are no sales figures listed in the company's annual report.
- Patents: The basic patent was applied for by Abbott in 1993.[257] Subsequently, Abbott applied for patents related to polymorphic forms of RTV[171, 258] and to a soft-gel capsule formulation.[259] These are due to expire respectively in 2019 and 2020.

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 capsule / tablet / ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

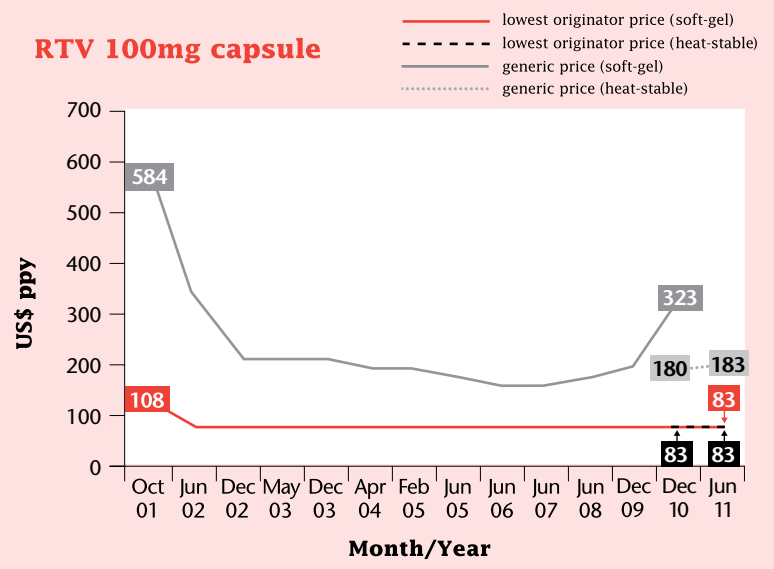
	Daily dose	Abbott		Matrix (CF)
		Category 1 countries	Category 2 countries	
Who can access this price?		See annex 2 & annex 8		See annex 2
RTV 80mg/ml oral solution	-	**(0.093/ml)**	No discounted price	
RTV 100mg soft-gel capsule (non heat-stable)	2*	**83 (0.114)**	No discounted price	
RTV 100mg tablet (heat-stable)	2*	**83 (0.114)**	No discounted price	**183 (0.250)**

*Dosing frequency depending on which drug ritonavir is used with as a booster.

(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

Evolution of the lowest price quoted for eligible developing countries since 2001:

As of May 2011, one generic source of RTV 100mg heat-stable tablet was quality-assured by WHO prequalification. Its price is shown here.



SPOTLIGHT ON ACCESS ISSUES

Ritonavir (RTV) is of crucial importance for the scaling-up and management of second-line treatment, as all protease inhibitors (PI) (with the exception of nelfinavir (NFV)), must be boosted with this drug.

Abbott developed a heat-stable fixed-dose combination of lopinavir and RTV (LPV/r) that was approved in the U.S. in 2005. However, it took until early 2010 – 12 years after its RTV soft-gel capsule first received regulatory approval – for Abbott to receive U.S. FDA and EMA approval for a heat-stable stand-alone RTV 100mg tablet.

The market authorisation of a heat-stable version of ritonavir as a separate pill finally put an end to the stranglehold by Abbott on the treatment options available to people living with HIV/AIDS. As a result of Abbott's inaction, many people living with HIV have been deprived of additional, improved and vital treatment options for many years. It also brought to an end the medical double standards the company has promoted by failing to prioritise the development of safer versions of its medicines.

The registration of this new formulation in developing countries will be crucial to allow the use of other PIs than LPV.

For the first time, a generic heat-stable RTV 100mg tablet was WHO prequalified in December 2010.

Patents

The basic patent on RTV could not be applied for in India as the country did not grant patents on medicines at the time. Nevertheless, Abbott has filed a number of patent applications and divisional applications on new forms of RTV that are pending before the Indian patent office.[174, 175, 176, 177] A pre-grant opposition to an application related to a polymorph of RTV[260, 261] was filed by civil society organisations in India in September 2006.[180] The outcome of this opposition will be crucial to the management of PI-based second-line treatment throughout the developing world.

Abbott abandoned a 2001 patent application including its divisionals on the RTV crystalline polymorph.[262] However, another relating to the RTV stable polymorph is still pending before the Indian patent office and warrants a pre-grant opposition to safeguard generic production.

Patents related to polymorphic forms of RTV have also been filed in other middle-income countries such as China and Brazil where they are pending. In Brazil, RTV is locally produced, as the basic patent is being opposed by Brazilian generic manufacturers in the courts.

In April 2010, Ecuador issued its first compulsory licence allowing Eskegroup SA, the local distributor for Cipla, to manufacture, offer for sale, sell, use or import RTV, or compositions including RTV, for public non-commercial use, against the payment of royalties to Abbott, until the patent expiration date in 2014.[264] The compulsory licence followed a decree by President Rafael Correa in October 2009, declaring access to essential medicines to be in the public interest of the population and allowing the national intellectual property office to issue compulsory licences to this end, based on Article 31 of the TRIPS Agreement.[265]

According to the Ministry of Health, the compulsory licence already has yielded savings of $150,000.

Paediatrics

RTV is approved for use in children from one month of age.[266]

A liquid formulation is available. However, the solution has a bitter aftertaste and contains 43% alcohol, and hence is not adapted for children. This limits the use of all protease inhibitors which require boosting with RTV and do not come in a paediatric fixed-dose combination.

The Paediatric Antiretroviral Working Group of WHO considers the development of a RTV 50mg heat-stable sprinkle or tablet to be a high priority.[22]