



# LOPINAVIR/ RITONAVIR (LPV/r)

## GENERAL INFORMATION

- Therapeutic class: boosted Protease Inhibitor (PI) in a double fixed-dose combination.
- Indicated for second-line, for adults, adolescents and children.<sup>8,137</sup>
- First approval by U.S. Food and Drug Administration (FDA): September 2000 (soft-gel capsules); October 2005 (heat-stable tablets).<sup>17</sup>
- Originator company and product brand name: Abbott Laboratories, Kaletra/Aluvia.
- Included in the 16th edition of the WHO Model List of Essential Medicines (EML).<sup>26</sup>
- World sales of originator product: 2009: US\$ 1.366 billion; 2008: \$1.47 billion; 2007: \$1.32 billion; 2004: \$897 million; 2003: \$754 million; 2002: \$551 million; 2001: \$292 million.<sup>145,146,147</sup>
- Most patents related to ritonavir (RTV) also cover LPV/r. The basic patent related to LPV was applied for by Abbott in 1996.<sup>148</sup>
- In addition, Abbott applied for patents more specifically related to LPV/r soft-gel capsules in 1997<sup>149</sup> which are due to expire in 2017. An application for a patent on the heat-stable tablet formulation was also filed in 2004,<sup>150</sup> which, if granted, would run until 2024.

## 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/dose of oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of April 2010) are in **bold**.

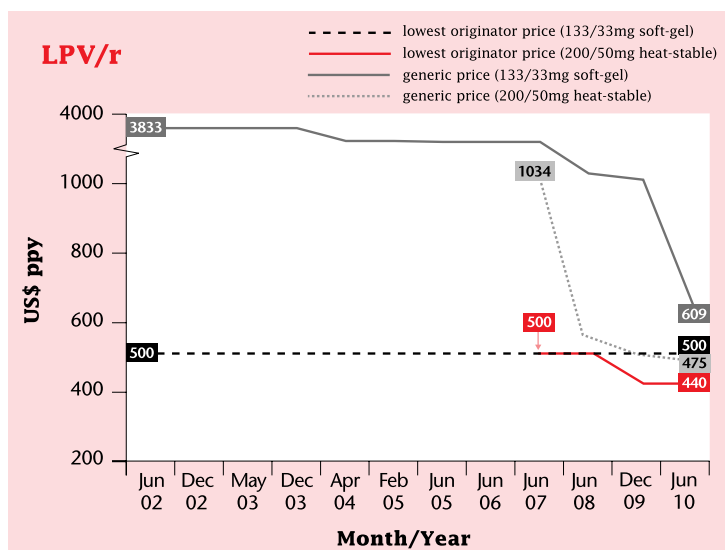
	Daily dose	Abbott		Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)
		Category 1 countries	Category 2 countries				
Who can access this price?		See annex 2 & annex 8		No restrictions			
LPV/r 80/20mg/ml oral solution	4 ml	<b>176 (0.121/ml)</b>	<b>400 (0.274/ml)</b>				
LPV/r 100/25mg heat-stable tablet	3	<b>165 (0.151)</b>	<b>376 (0.343)</b>	<b>219 (0.200)</b>			<b>228 (0.208)</b>
LPV/r 133/33mg soft-gel capsule	6	<b>500 (0.228)</b>	<b>1000 (0.457)</b>		609 (0.278)		
LPV/r 200/50mg heat-stable tablet	4	<b>440 (0.301)</b>	<b>1000 (0.685)</b>	<b>475 (0.325)</b>	463 (0.317)	493 (0.338)	<b>486 (0.333)</b>

(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 quoted price for developing countries since 2002:

As of April 2010, there was no generic source of LPV/r 133/33mg soft-gel capsule included in the WHO List of Prequalified Medicinal Products, so the lowest priced generic is considered in this graph. There were however two generic sources of LPV/r 200/50mg heat-stable tablet included in the list. The one with the lowest price is shown here.

The generic price of LPV/r 200/50mg heat-stable tablet has decreased by 54% since 2007.



## SPOTLIGHT ON ACCESS ISSUES

In December 2009, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).<sup>9</sup>

The heat-stable formulation of LPV/r manufactured by Abbott and Indian generic companies is now marketed in developing countries. In comparison to the older, soft-gel capsule formulation, the new formulation has a lower pill count (reducing the burden from six to four pills per day), there is no need for refrigeration, and there are no dietary restrictions. It is now approved as once-a-day dosing in treatment-experienced patients with fewer than three lopinavir resistance-associated mutations.<sup>17</sup> This should enhance adherence. However, pill burden remains an issue.

The entry of generic manufacturers is having a positive effect on the market, and prices are declining. The Clinton Foundation's most recent announcement has some generic manufacturers offering prices of US\$ 440 per patient per year (see annex 13 for details).

### Patents

In India, Abbott has applied for several patents on the solid dosage formulation and polymorphic forms of lopinavir (LPV), ritonavir (RTV) and on the heat-stable combination of LPV/r, a number of which have been opposed by civil society organisations<sup>151</sup> and generic companies. Following a pre-grant opposition to the application related to the soft-gel formulation of LPV/r, the application was withdrawn by the company. Other oppositions are pending decisions by the Indian patent office.

If one of these patent applications is granted, current generic competition, which is bringing prices substantially down as demand increases, will be under threat.

India and other countries could issue compulsory licences to enable unrestricted competition from generic manufacturers to continue.

In Thailand, where Abbott holds patents, the price of LPV/r was US\$ 2,200 ppy in 2007. In January 2007, the Ministry of Public Health issued a compulsory licence to import more affordable generic versions of the drug from India.<sup>53</sup> Thailand faced fierce criticism from developed countries and multinational pharmaceutical companies and Abbott's response was to withdraw all registration applications in Thailand for its new products, including the heat-stable LPV/r. Thailand today imports generic LPV/r from India for \$793 ppy.<sup>54</sup>

In response to Thailand's compulsory licence, Abbott reduced the price for 40 middle-income countries for both the soft-gel and the heat-stable version to \$1,000 ppy, including Brazil which at the time was paying \$1,380.<sup>152</sup>

Indeed, the basic patent for LPV/r is protected in Brazil under the so-called 'pipeline mechanism', a provision in Brazilian patent law deemed to be in excess of the minimum standards for intellectual property protection under the TRIPS Agreement.

In 2007, the National Federation of Pharmacists (Fenafar) – on behalf of the Brazilian Network for the Integration of Peoples (Rebrip) - requested the Brazilian Prosecutor General consider overturning the pipeline mechanism as unconstitutional. They argue that these patents should not be granted in Brazil on the basis that they had not gone through the regular analysis process for patent applications and that they go against the public interest. In 2009, the Prosecutor General lodged a case for unconstitutionality with the Supreme Court. MSF-Brazil is actively following the case.<sup>153</sup>

### Paediatrics

LPV/r is approved for use in children from two weeks old.<sup>17</sup>

In early 2007, Abbott released a paediatric LPV/r 100/25mg heat-stable tablet. While this new formulation is welcome, it does not help the youngest patients, as the tablet is 15mm long and cannot be crushed, leaving this formulation unsuitable for children who cannot swallow tablets.

The alternative for these small children is a solution that requires refrigeration until dispensing, after which it must be stored below 25°C for no more than six weeks. Furthermore, the solution consists of 42% alcohol and has a very unpleasant taste.

There is an urgent need for more adapted heat-stable paediatric formulation of LPV/r (such as soluble granules or sprinkles) for young children who can not swallow the existing tablet. A heat-stable sprinkle in a paediatric dose is under development by generic companies. The Paediatric Antiretroviral Working Group of WHO considers the development of a LPV/r 40/10mg heat-stable sprinkle to be a high priority.<sup>137</sup>

Today there are two generic sources of heat-stable LPV/r 100/25mg included in the WHO List of Prequalified Medicinal Products.

Recent changes in the WHO guidelines recommending that all HIV-positive children under one year of age start ARV therapy as soon as possible regardless of clinical status, combined with the recommendation to start all children exposed to nevirapine on a PI-based regimen, should result in an increased demand for this combination for very young children.<sup>130</sup>