

# LOPINAVIR/ RITONAVIR (LPV/r)

## GENERAL INFORMATION

- Therapeutic class: Boosted protease inhibitor (PI) in a double fixed-dose combination.
- WHO guidelines: Indicated for second-line, for adults, adolescents and children.<sup>6,22</sup>
- Originator company and product brand name: Abbott, Kaletra/Aluvia.
- First approval by U.S. Food and Drug Administration (FDA): September 2000 (soft-gel capsules); October 2005 (heat-stable tablets).<sup>23</sup>
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- World sales of originator product: 2010: US\$1.26 billion; 2009: \$1.37 billion; 2008: \$1.47 billion; 2007: \$1.32 billion; 2004: \$897 million; 2003: \$754 million; 2002: \$551 million; 2001: \$292 million.<sup>166, 167, 168, 169</sup>
- Patents: Most patents related to ritonavir (RTV) also cover LPV/r. The basic patent related to LPV was applied for by Abbott in 1996.<sup>170</sup> In addition, Abbott applied for patents more specifically related to LPV/r soft-gel capsules in 1997<sup>171</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>172</sup> which could potentially run until 2024, in countries where granted.

## 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**.

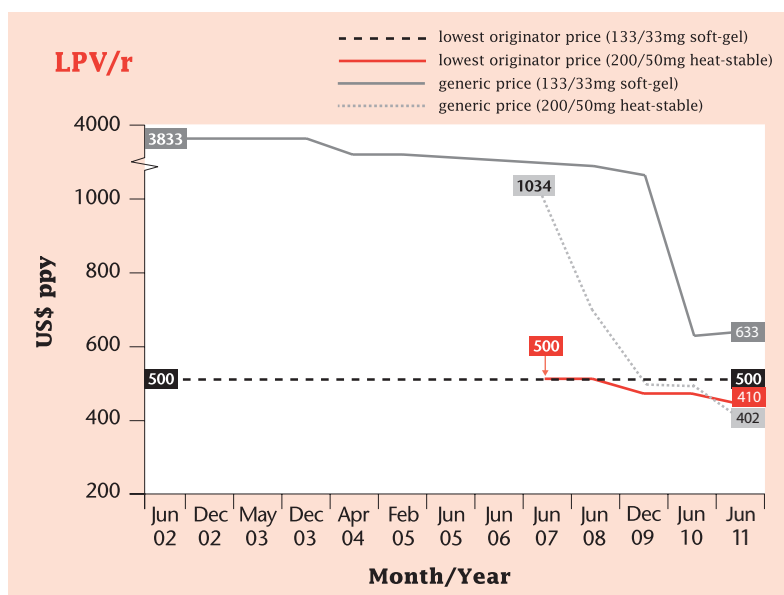
	Daily dose	Abbott		Aurobindo (CF)	Cipla (CF)	Hetero	Matrix (CF)
		Category 1 countries	Category 2 countries				
Who can access this price?		See annex 2 & annex 8		See annex 2			
LPV/r 80/20mg/ml oral solution	4 ml	<b>164 (0.112/ml)</b>	<b>400 (0.274/ml)</b>		256 (0.175/ml)		
LPV/r 100/25mg tablet (heat-stable)	3	<b>153 (0.140)</b>	<b>376 (0.343)</b>	<b>175 (0.160)</b>			<b>164 (0.150)</b>
LPV/r 133/33mg soft-gel capsule (non heat-stable)	6	<b>500 (0.228)</b>	<b>1000 (0.457)</b>		633 (0.289)		
LPV/r 200/50mg tablet (heat-stable)	4	<b>410 (0.281)</b>	<b>1000 (0.457)</b>	<b>438 (0.300)</b>	<b>499 (0.342)</b>	493 (0.338)	<b>402 (0.275)</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 May 2011, there was no generic source of LPV/r 133/33mg soft-gel capsule quality-assured by US FDA or WHO prequalification, so the lowest-priced generic is shown in this graph. There were however three quality-assured generic sources of LPV/r 200/50mg heat-stable tablet. The one with the lowest price is shown here.

The generic price of LPV/r 200/50mg heat-stable tablet has decreased by 61% since 2007.



## SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO recommendations for second-line therapy included two 'preferred' protease inhibitors (PI), to be taken in combination with two NRTIs. They are lopinavir/ritonavir (LPV/r) and atazanavir (ATV) boosted with ritonavir (RTV).<sup>7</sup> With its once-a-day dosing ATV is the more patient-friendly PI of the two.

The heat-stable formulation of LPV/r manufactured by Abbott and Indian generic companies is now marketed in developing countries. In comparison with 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>23</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. However Abbott's sales of this drug dominates the developing world where it captured 81% of the market share in 2008.<sup>16</sup>

### Patents

In India, Abbott has applied for several patents on the polymorphic forms of LPV<sup>173</sup> and RTV,<sup>174, 175, 176, 177</sup> on the combination of LPV/r in a tablet formulation,<sup>178, 179</sup> and on the LPV process. A number of these applications have been opposed by civil society organisations<sup>180</sup> and generic companies.

Following a pre-grant opposition to the application related to the tablet formulation of LPV/r, the

application was rejected by the Indian patent office.<sup>181</sup> While an appeal is pending to the rejection, Abbott has abandoned the two divisional patent applications it had filed on the tablet formulation of LPV/r.<sup>182, 183</sup> The Indian patent office also rejected a patent application on lopinavir crystalline polymorphs.<sup>184</sup>

In a welcome move, Abbott has also abandoned several applications including the divisional on the RTV crystalline polymorph. However, key applications, relating to the RTV stable polymorph,<sup>185</sup> the solid pharmaceutical dosage (tablet) formulation of LPV/r,<sup>179</sup> and to the LPV process<sup>186</sup> are still pending before 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 urgently issue compulsory licences to enable unrestricted competition from generic manufacturers to continue.

In Thailand, where Abbott holds patents, the price of LPV/r was \$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>124</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>125</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>3</sup>

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) – made a request to the Brazilian Prosecutor General to consider overturning the pipeline mechanism on the grounds that it is unconstitutional. A key argument in favour of overturning the mechanism is that these patents should not be granted in Brazil, since they were already in the public domain and that granting the patents in this way is against the public interest. In 2009, the Prosecutor General lodged a case for unconstitutionality with the Supreme Court.<sup>187</sup> MSF-Brazil is actively following the case.<sup>188</sup>

In 2005, the Brazilian government entered into negotiations with Abbott to reduce the price of LPV/r and in June of the same year, the Ministry of Health declared the drug to be of public interest, which is the first step towards issuing a compulsory licence. However, in October 2005 an agreement between Abbott and the government was signed.