LOPINAVIR/RITONAVIR (LPV/r)

GENERAL INFORMATION

- **Therapeutic class**: Boosted protease inhibitor (PI) in a double fixed-dose combination.
- **2016 WHO Guidelines:** LPV/r is recommended for first-line treatment for all HIV-positive children under three years of age, regardless of NNRTI exposure. LPV/r is also indicated as part of second-line treatment for adults, including pregnant and breast-feeding women, and children.
- Originator company and product brand name: Abbott; Kaletra or Aluvia. In 2013, Abbott separated into two companies, Abbott and AbbVie; Abbvie holds the portfolio for most pharmaceuticals, including Kaletra.
- First approved by US Food and Drug Administration (FDA): September 2000 for soft-gel capsules; October 2005 for heat-stable tablets.
- WHO Model List of Essential Medicines (EML): Included in the 19th edition for adults and the 5th edition for children.
- World sales of originator product: 2015: US$700 million; 2014: $870 million; 2013: $962 million; 2012: $733 million; 2011: $1.2 billion; 2010: $1.3 billion; 2009: $1.4 billion; 2008: $1.5 billion; 2007: $1.3 billion; 2004: $897 million; 2003: $754 million; 2002: $551 million; 2001: $292 million.[1]

PRICE INFORMATION

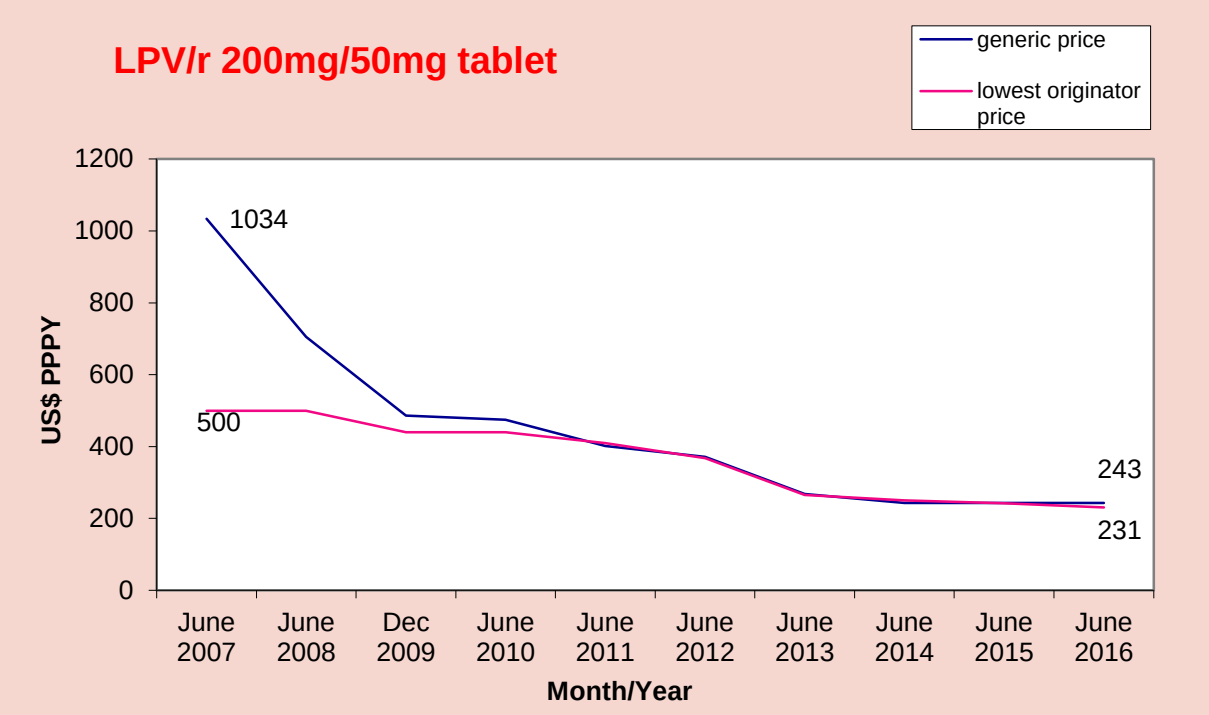
Developing country prices in US$ per person per year (pppy), as quoted by companies.

The price in brackets corresponds to the unit price of one capsule/tablet/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2016) are in **bold.**

	Daily Dose	AbbVie		Aurobindo	Cipla	Hetero	Macleods
		Category 1 countries	Category 2 countries				
LPV/r 80/20mg/ml oral solution (paediatrics)	4ml	**150 (0.103)**	**296 (0.203)**				
LPV/r 40/10mg capsule (paediatrics)	xx				**(0.160)**		
LPV/r 100/25mg heat-stable tablet (paediatrics)	3	**108 (0.099)**	**278 (0.254)**	**151 (0.138)**	155 (0.142)		**143 (0.131)**
LPV/r 200/50mg heat-stable tablet	4	**231 (0.158)**	**740 (0.507)**	**243 (0.167)**	**268 (0.183)**	**280 (0.192)**	**293 (0.201)**

Evolution of the lowest price quoted for eligible developing countries:

In 2014, the price of generic LPV/r 200/50mg tablets came down to $243 pppy, and seems to have stabilized there. The price of originator LPV/r is slightly lower, at $231 pppy; in South Africa, where AbbVie is the only supplier, the price for LPV/r is lower – as of July 2016, it is $182 pppy.[2]



SPOTLIGHT ON ACCESS ISSUES

There are four WHO-prequalified suppliers of generic LPV/r tablets for adults (200mg/50mg).

In 2015, despite the number of suppliers in the international market, there was a significant LPV/r stockout across South Africa. MSF reported that 65% of people were sent away without any medicine, while 35% only received a partial supply,[3] leaving them vulnerable to drug resistance and treatment failure. The LVP/r supply is likely to remain unstable, since AbbVie has been undercutting generic competition with slightly lower prices. This has made it difficult for generics to enter the market in countries including South Africa, where Abbvie held the patent for LPV/r until a recent agreement with the Medicines Patent Pool (MPP) in December 2015; Aurobindo, Desano and Emcure have recently signed the VL through the MPP on the adult formulation, and Hetero has signed on the paediatric formulation.[4,5]

Paediatrics: There are currently three WHO-prequalified, approved suppliers of generic LPV/r tablets for children (100 mg/25 mg). In June 2015, Cipla received FDA approval for a new pellet formulation of LPV/r, but they are not yet commercially available. Cipla is the only WHO prequalified manufacturer of the oral solution, but it is no longer in production, leaving children who are under three years old with no option except the originator product until the new pellet formulation becomes available.

LPV/r pellets are a far more favourable formulation than the oral solution, which contains 40% alcohol, tastes very bitter, and requires a cold chain, but the price of the pellets may be a barrier in some countries. LPV/r

pellets cost $19.20 for a bottle of 120. For a 10kg child, at a dose of eight capsules per day (which equates to two bottles per month), the price is $460.80 pppy, compared to $150 pppy for oral solution, or $108 pppy for paediatric tablets.

Countries are likely to recognise the benefits of LPV/r pellets, especially for younger children. To ensure better access to the LPV/r pellets, Cipla needs to reduce the price so that it is at least on par with the oral solution. Further modification of the pellets to produce a taste-masked formulation is underway, since the bitter taste remains.

PATENTS

(Patent information may be updated in 2016 to fully reflect the evolving landscape of patents, other forms of intellectual property, licensing and use of flexibilities for the particular drug.)

Most patents related to ritonavir (RTV/r) also cover LPV/r. Abbott applied for the basic patent related to lopinavir (LPV) in 1996.[6] In addition, Abbott applied for patents more specifically related to the LPV/r soft-gel capsules in 1997,[7] which are due to expire in 2017. An application for a patent on the LPV/r heat-stable tablet formulation that is now widely used in developing countries was filed in 2004;[8,9] it could potentially run until 2024.

Access in Developing Countries

Abbott could not file a patent on the base compound of LPV in countries which did not grant patents on pharmaceuticals before the full implementation of the TRIPS agreement, such as India. Competition from Indian generics manufacturers has, together with increased global demand, brought down the price of LPV/r in some countries.

However, Abbott applied for several other patents in India, including polymorphic forms of LPV and RTV[10,11,12] the combination of LPV/r,[13] and the process of making LPV.[14] These patents have all been rejected by the India patent office or abandoned by Abbott,[9,15,16,17] following a series of pre-grant oppositions filed by civil society organisations or generics producers.[17]

Another patent application is on the solid pharmaceutical dosage (tablet) formulation of RTV.[18] This application is pending. Pre-grant oppositions have been filed by generics producers and India Network of People Living with HIV/AIDS since 2013.[19] If this patent application is granted, current generic competition on LPV/r could be under threat.

In Thailand, where Abbott holds patents on LPV/r and the drug was costly, the Ministry of Public Health issued a compulsory licence in January 2007 to import more affordable generic versions of the drug from India.[20] Thailand faced fierce criticism from developed countries and multinational pharmaceutical companies for the decision. Abbott's response was to withdraw all applications to register its new products in Thailand, including heat-stable LPV/r, which triggered heavy criticism of Abbott from civil society worldwide.[21]

In Brazil, more than 70,000 HIV-positive people use LPV/r. The original patent on the drug is about to expire, but AbbVie, the current patent holder, is using many strategies to extend their monopoly. GTPI, a civil society coalition, filed a patent opposition in 2011[22] to prevent the grant of a patent (PI 0413882-1) that would extend the monopoly from 2016 to 2023. In 2013, the patent application was rejected by ANVISA and later by INPI (Instituto Nacional da Propriedade Industrial), Brazil's Institute of Intellectual Property. However, the company has filed multiple appeals, including in the courts, where it managed to obtain decisions that

undermine the rejection. GTPI has also filed an amicus curiae brief at the Supreme Court and a final decision is still pending.[23]

In November 2011, several public health groups – including Public Citizen – launched a global campaign across 12 countries to challenge Abbott's patents on LPV/r, using patent oppositions or requests for compulsory licences. In September 2012, the Indonesian government issued compulsory licences on several key ARVs, including LPV/r. This licence will last until the patent expires in August 2018.[24] In Ecuador, where a compulsory licence was originally issued on RTV, the government has been evaluating a new licence request regarding the LPV/r patent.[25] However, upon a bilateral free trade agreement signed with the European Union in 2014, several requests for compulsory licences have been withdrawn by Ecuador's public pharmaceutical firm, after four compulsory licences were previously issued on pharmaceuticals the same year.[26]

MPP Licence, including its limitations

In December 2014, AbbVie entered into a licence agreement with the MPP on the paediatric formulations of LPV/r and RTV.[27] The licence is royalty-free and generics manufacturers from any country can join. The AbbVie licence with the MPP covers 102 developing countries, but it excludes a number of countries, including Argentina, Brazil, China and Ukraine. Generic access is possible for excluded countries if patents are not in force – as in India, where the patent was withdrawn – or if the countries use compulsory licensing.

The MPP-AbbVie licence covers both the liquid formulation of LPV/r and the 40mg/10mg pellet formulation[28] that are used for children under three years of age. But the licence does not cover the paediatric 100mg/25mg tablet, which is needed for children over three years of age. This has left a significant gap for all paediatric patients who need the right formulation for effective treatment.

AbbVie's licence has had a chilling effect on registration of the 100mg/25mg paediatric tablet, affecting its availability in countries where Abbott holds a number of patents on lopinavir and ritonavir. Since a double dose of the paediatric tablet could be used by adults, AbbVie's strategy also helps maintain their monopoly on adult formulations.

Moreover, before the full implementation of the licence by generics producers, access to generic versions of the two paediatric formulations of LPV/r remain absent.[29] At the time of going to press in July 2016, only one Indian generics company, Hetero, has signed the sub-licence for the paediatric formulations, but full registration and supply to the market will still take time to be realised.[30]

In December 2015, AbbVie entered into a new licence agreement with the MPP on the adult formulation of LPV/r; it covers all countries in Africa.[31] Due to its defined geographic coverage, people in all countries outside of Africa remain excluded where patents are currently in force, unless other legal and policy measures are used (such as issuing a compulsory licence). For instance, with the compulsory licence on LPV/r, Thailand has secured more affordable generic versions of LPV/r, and can continue to do so from companies that sign the voluntary licence, whilst neighbouring countries such as Malaysia will remain unable to access affordable versions of LPV/r. In July 2016, the MPP announced its newly signed sublicence agreements with the Chinese generics company Desano, and the Indian generics companies Emcure and Aurobindo for the adult formulation.[4]

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