

# ATAZANAVIR (ATV)

## GENERAL INFORMATION

- Therapeutic class: Protease inhibitor (PI).
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.<sup>24</sup>
- Patents: The basic patent was filed in April 1997 by Novartis and is expected to expire in April 2017.<sup>50</sup> Bristol-Myers Squibb is manufacturing ATV under licence from Novartis. BMS also applied for patents on the crystalline bisulfate salt of ATV in December 1998<sup>51</sup> and on a process for preparing the bisulfate salt and novel forms in 2005.<sup>52</sup>
- WHO guidelines: Boosted ATV is indicated for second-line for adults and adolescents.<sup>6</sup>
- World sales of originator product: 2010: US\$ 1.5 billion; 2009: \$1.4 billion; 2008: \$1.3 billion; 2007: \$1.1 billion; 2006: \$931 million; 2005: \$696 million; 2004: \$369 million; 2003: \$81 million.<sup>44, 45, 116, 47, 48, 49</sup>
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Reyataz.
- First approval by U.S. Food and Drug Administration (FDA): June 2003.<sup>23</sup>

## 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. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

	Daily dose	BMS		Emcure (CF)	Matrix (CF)
		Category 1 countries	Category 2 countries		
Who can access this price?		See annex 2 & annex 7		See annex 2	
ATV 100mg capsule	3*			<b>(0.267)</b>	
ATV 150mg capsule	2*	<b>412 (0.565)</b>	<b>547 (0.749)</b>	<b>268 (0.367)</b>	<b>426 (0.583)</b>
ATV 200mg capsule	-	(0.677)	(0.942)	<b>(0.483)</b>	
ATV 300mg capsule	1*			<b>268 (0.733)</b>	<b>250 (0.686)</b>

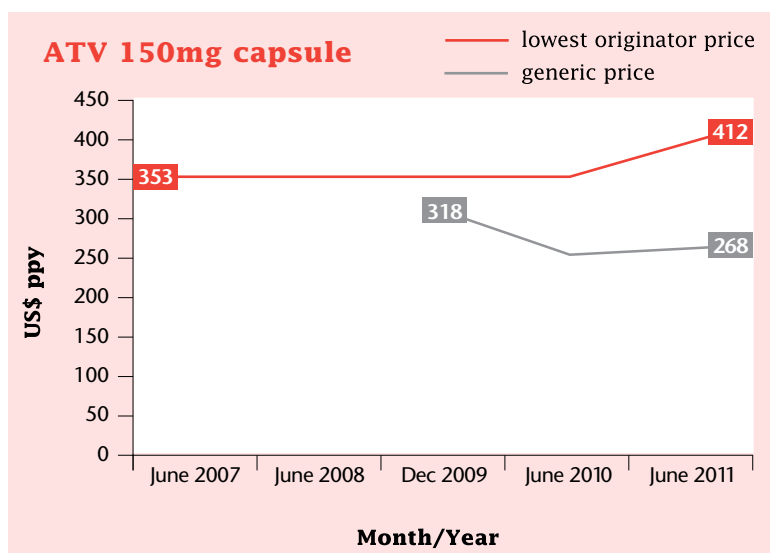
\*The dose of ATV must be boosted with RTV 100mg once a day in treatment experienced patients.

(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 2007:

As of May 2011, two generic sources of ATV 150mg capsule were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Last year, for the first time since 2007, the originator price increased by 17%, while generic prices have dropped by 16% since 2009.



Continued overleaf ❖

## 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 atazanavir (ATV) boosted with ritonavir (RTV) and lopinavir/ritonavir (LPV/r).<sup>7</sup> With its once-a-day dosing ATV is the more patient-friendly PI of the two.

ATV, like all PIs (with the exception of nelfinavir (NFV), requires boosting with RTV. Abbott's heat-stable ritonavir received marketing approval in the U.S. and Europe in early 2010. Registering this new formulation in developing countries will be crucial in order to allow the use of other PIs than lopinavir. A generic heat-stable RTV is now available and was WHO prequalified in late 2010.

As ATV is one of the two PIs recommended by WHO, there is an urgent need for generic manufacturers to supply a heat-stable ATV/r fixed-dose combination. Currently this fixed-dose combination is not produced by the originator companies.

In some African countries including Ethiopia, Ghana, Kenya, Nigeria, Tanzania and Uganda, Bristol-Myers Squibb (BMS) discontinued all commercial activities by the end of 2009, including deregistration of all BMS products.<sup>53</sup>

### Patents

In most developing countries with generic pharmaceutical production capacity, including Brazil, China and India, Novartis and BMS filed patent applications related to the ATV compound,<sup>54</sup> bisulphate salt,<sup>55</sup> which is the best route to making ATV<sup>56</sup> and its combination with other ARVs.<sup>57, 58, 59, 60</sup> Most patents have been granted in Brazil and China.

In India, where ATV is already under generic production, patent applications are still under examination. Civil society organisations filed a pre-grant opposition<sup>61</sup> to Novartis's basic patent application<sup>62</sup> on the grounds of lack of novelty.<sup>63</sup> The patent application has since been abandoned,<sup>64</sup> but several divisional patent applications<sup>65, 66</sup> have been filed by Novartis. In

addition, a single patent application filed by BMS in 2006 contained claims that covered the most efficient route of manufacturing ATV and its bisulphate salt.<sup>67</sup> This application was opposed by generic companies and the patent office recently rejected the application.<sup>68</sup> However, BMS had already filed a divisional patent application<sup>69</sup> which is pending before the Indian patent office. These divisional and other patent applications on ATV and its use in combination with other ARVs<sup>70, 71, 72, 73</sup> warrant additional pre-grant oppositions.<sup>74</sup>

In addition, Abbott has filed patent applications on RTV in India and other developing countries which, if granted, will block the development of and access to generic ATV/r fixed-dose combinations.

In February 2006, BMS granted technology transfer and voluntary licences to two generic manufacturers (Emcure and Aspen) to manufacture and sell ATV. In February 2008, Emcure received US FDA tentative approval for the 100mg, 150mg and 200mg ATV capsules. Under the terms of the licences, however, sales of these products are royalty-free but are restricted to sub-Saharan Africa. BMS has a separate agreement with Emcure that covers India.<sup>75</sup>

Licensing agreements in India should not be necessary if patent oppositions are successful. If patents are granted, India and other countries could issue compulsory licences to enable unrestricted competition from generic manufacturers, in order to bring prices down, increase access and facilitate the development of an ATV/r fixed-dose combination.

BMS's differential pricing structure is limited to sub-Saharan Africa and low-income countries. This structure leaves middle-income countries such as Brazil paying more than \$1,000 per patient per year, a prohibitive price for many of these countries.<sup>76</sup>

In Brazil, BMS's monopoly led to shortages of ATV in 2005<sup>77</sup> and 2011,<sup>78</sup> and several patients had to change

treatment regimens. Civil society groups then urged the government to issue a compulsory licence (CL) arguing Brazilian law justified the measure.<sup>79</sup> After the second shortage however, the government announced the creation of a public-private partnership for the local production of ATV,<sup>80</sup> preferring to negotiate with BMS rather than issue a CL to stimulate the local production of more affordable generic versions. The reasons for this choice remain unclear, and civil society groups continue to demand transparency on this agreement, particularly since it involves a publicly-owned laboratory.<sup>81</sup> To date, no information concerning price reductions or sales restrictions for this product has been made available.

In 2011, a year's treatment using the 300mg tablet in Brazil cost \$1,022. By April 2011, around 40,450 patients in Brazil were taking ATV as part of their treatment regimen.<sup>82</sup>

### Paediatrics

In March 2008, ATV was approved for use in children between six and 18 years of age.<sup>23</sup> No formulation exists for children.

In addition, ATV must be given with a RTV booster, but the RTV solution currently available has a bitter aftertaste and contains 43% alcohol, and is thus not adapted for children, limiting the use of ATV in this population.

In 2008, WHO recommended early treatment for all HIV-positive children, and children who have been exposed to nevirapine (NVP) either through their mother or through a single dose in a prevention of mother-to-child transmission programme. WHO recommends these children should be started on a PI-based regimen.<sup>22</sup> Today, the only option for these children is the LPV/r formulation.

To simplify treatment for all children, there is an urgent need for studies on ATV to be completed in infants and children under six, and child-adapted formulations of ATV and ATV/r to be made available.