

ZIDOVUDINE/ LAMIVUDINE (AZT/3TC)

GENERAL INFORMATION

- Therapeutic class: Two NRTI in a double fixed-dose combination.
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.^{6,22}
- Originator company and product brand name: GlaxoSmithKline (GSK), Combivir. In April 2009, Pfizer and GSK jointly announced the creation of ViiV, a new joint venture focusing solely on the R&D and commercialisation of HIV medicines.
- First approval by U.S. Food and Drug Administration (FDA): September 1997.²³
- WHO Model List of Essential Medicines (EML): Included in the 17th edition. The WHO Expert Committee on the Selection and Use of Essential Medicines recommends and endorses the use of fixed-dose combinations and the development of appropriate new fixed-dose combinations.²⁴
- World sales of originator product: 2010: US\$ 588 million; 2009: \$649 million; 2008: \$713 million; 2007: \$888 million; 2006: \$1 billion; 2005: \$1.1 billion; 2004: \$1.1 billion.^{163, 25, 26, 27, 28, 29, 30}
- Patents: Most patents related to zidovudine (AZT) or to lamivudine (3TC) also affect this combination. In addition, GSK applied for patents specifically related to the use of AZT and 3TC in combination,³¹³ and for the tablet formulation of the FDC,³¹⁴ which are due to expire in 2012 and 2017, respectively.

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

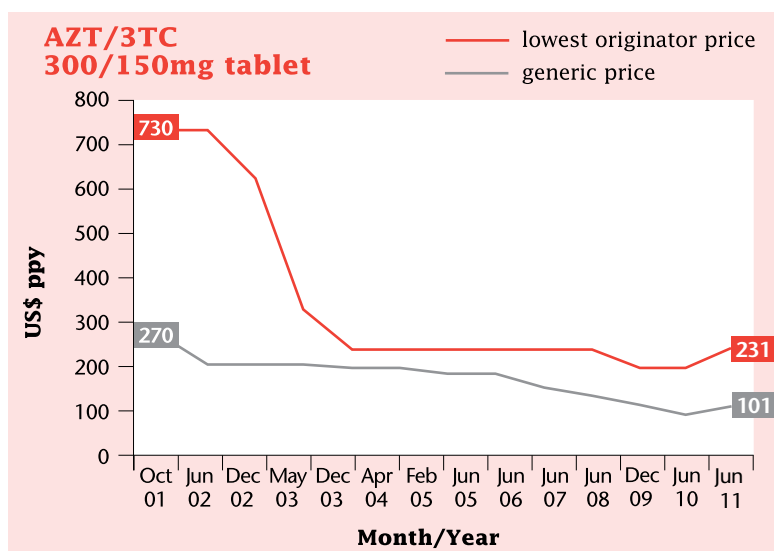
	Daily dose	ViiV	Aurobindo (CF)	Cipla (CF)	Hetero (CF)	Matrix (CF)	Micro Labs (CF)	Ranbaxy (CF)	Strides	Varchem
Who can access this price?		See annex 2								
AZT/3TC 60/30mg tablet	4		92 (0.063)			73 (0.050)		88 (0.060)		
AZT/3TC 300/150mg tablet	2	231 (0.316)	107 (0.147)	104 (0.142)	110 (0.150)	101 (0.138)	112 (0.154)	110 (0.150)	123 (0.169)	107 (0.147)

(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 developing countries since 2001:

As of May 2011, 11 generic sources of AZT/3TC 300/150mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Since 2001, the originator price has decreased by 68%, while generic prices have dropped by 63%.



SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. These new recommendations advise countries to phase out stavudine- (d4T) based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir- (TDF) based first-line regimens.

For many years, the regimen containing d4T played a crucial role in ART scale-up in resource-limited settings, due to its availability in a fixed-dose combination and most importantly its low cost. d4T remains a widely used ARV in first-line regimens.

AZT is also recommended for second-line treatment if tenofovir has been used in first-line. AZT should then be used as the NRTI backbone, in combination with either lamivudine (3TC) or emtricitabine (FTC), to which a boosted protease inhibitor (PI) should be added.

In 2011, ViiV clarified their pricing structure (see annex 2), confirming that their standardised price discounts were not in fact available to all fully-financed Global Fund or PEPFAR programmes, contrary to previous announcements. Global Fund financed programmes in middle-income countries have not been and will not be eligible for those prices, and will have to negotiate prices on a case-by-case basis.

Patents

This combination was produced by Indian generic companies because none of the individual components was patented in India. However, these generic versions came under threat when India began granting patents on pharmaceuticals in 2005, as GSK had applied for a patent on the combination.^{315, 316}

Civil society organisations in India opposed the patent application in March 2006,³¹⁷ which resulted in GSK communicating in August 2006 that patents specifically related to the fixed-dose combination were being withdrawn in all countries.³¹⁸

Yet in some countries, generic versions of the FDC are not available because of GSK patent rights. In China, for example, GSK's exclusive rights on 3TC alone have led to the fact that only the originator product is available at \$1,839 per patient per year.

Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends AZT/3TC as one of the possible combinations to be given with either an NNRTI or a PI in the first-line. The combination can also be part of second-line regimens, depending on what has been used as a first-line.²²

AZT/3TC, when used with NVP, is part of one of the two most commonly used first-line regimens

for children today (the other being d4T/3TC/NVP). With both of these regimens, there is a need to start NVP at a lower dose for the first two weeks to minimise the side effects. Quality-assured double fixed-dose combinations are therefore of great value in allowing children to be safely and accurately dosed while starting treatment. In their absence, the alternative is to use two different syrups, which can be difficult to administer.

Because of the long-term risks of toxicity, particularly lipodystrophy in children treated with d4T-containing regimens, the use of AZT is preferred. Toxicity risks are also associated with AZT, with possible anaemia developing over the first few months of therapy, but the drug remains much better tolerated than d4T.²² WHO guidelines recommend a preferential order of NRTIs to be used in first-line regimens, with AZT preferred over ABC, and ABC preferred over d4T.

As of May 2011, two paediatric AZT/3TC fixed-dose combination tablets were quality-assured by either US FDA or WHO prequalification.