

STAVUDINE (d4T)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.²⁴
- WHO guidelines: Indicated for first-line for children. WHO 2009 guidelines also recommended to move away from d4T first-line in adults and adolescents.^{6,22} WHO updated the 2006 guidelines to recommend a reduction in dose of d4T 40mg to d4T 30mg for all weight categories of patients.²²
- World sales of originator product: 2006: US\$ 155 million; 2005: \$216 million; 2004: \$272 million; 2003: \$354 million. After 2006, there are no sales figures listed in the company's annual report.^{48,100}
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Zerit.
- Patents: d4T was the result of U.S. public sector research. It was originally synthesised by the Michigan Cancer Foundation in 1966 under a grant from the National Cancer Institute.²⁷³ Researchers from Yale University then discovered its antiretroviral activity and applied for a patent in December 1987, mostly in developed countries, for the use of d4T to treat patients infected with retroviruses.²⁷⁴ Patent protection was extended until the end of 2008 in the U.S. and until 2011 in most European countries. BMS markets d4T under a marketing and distribution licence from Yale University. Patents should have expired in most other countries at this point.
- First approval by U.S. Food and Drug Administration (FDA): December 1994.²³

PRICE INFORMATION

Developing country prices in US\$ per patient per year, as quoted by companies.

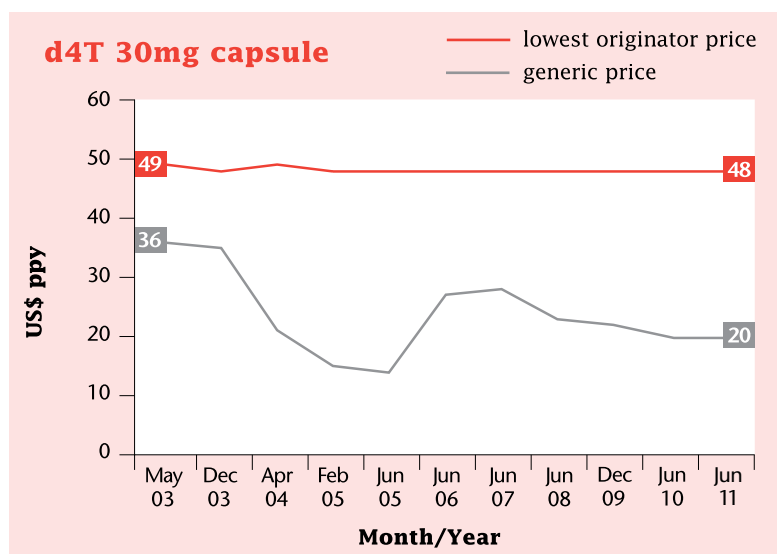
The price in brackets corresponds to the price of one capsule/ml of oral solution. Products quality-assured by US FDA or WHO prequalification (as of May 2011) are in **bold**.

| | Daily dose | BMS | | Aspen | Aurobindo (CF) | Cipla | Hetero | Ranbaxy | Strides |
|-------------------------------------|------------|-----------------------|----------------------|----------------|----------------------|----------------------|-------------------|-------------------|-------------------|
| | | Category 1 countries | Category 2 countries | | | | | | |
| Who can access this price? | | See annex 2 & annex 7 | | See annex 2 | | | | | |
| d4T 1mg/ml powder for oral solution | 20 ml | 58 (0.008/ml) | | | 58 (0.008/ml) | 51 (0.007/ml) | | | |
| d4T 15mg capsule | - | (0.083) | (0.118) | (0.027) | (0.024) | | (0.025) | | |
| d4T 20mg capsule | - | (0.094) | (0.118) | (0.031) | (0.025) | | (0.028) | | |
| d4T 30mg capsule | 2 | 48 (0.066) | 86 (0.118) | | 20 (0.027) | | 21 (0.029) | 24 (0.033) | 22 (0.030) |

(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.

Continued overleaf ❖

Stavudine (d4T) continued



Evolution of the lowest price quoted for developing countries since 2003:

As of May 2011, seven generic sources of d4T 30mg capsule were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

The first generic source of d4T 30mg capsule was quality-assured by WHO prequalification in June 2005 – the generic price in the graph above corresponds to the lowest generic price until that date, and to the lowest quality-assured generic price from that date on.

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 has 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.

During the review of the marketing authorisation of this medicine in February 2011, the European Medicines Agency (EMA) decided to severely restrict its use in both adults and children, recommending that in view of its long-term toxicities, d4T be used for as short a time as possible and only when no appropriate alternatives⁸ exist.

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.²⁷⁶ BMS also discontinued the marketing of d4T products in South Africa in December 2010.

Patents

Yale University did not apply for patents in most developing countries except for South Africa. Generic manufacturers from countries with manufacturing capacity, such as Brazil, China, India or Thailand could therefore legally manufacture and export affordable generic versions of d4T.

In South Africa, where BMS marketed d4T under an exclusive licence from Yale, the drug was 34 times more expensive than generic versions available in other countries. This prompted controversy in March 2001, particularly as the medicine had been developed with public funds. After pressure from researchers, students, and access advocates, Yale renegotiated its licence with BMS to allow the importation of more affordable generic versions of d4T to South Africa.²⁷³

Paediatrics

d4T is approved for use in children.²⁷⁷ In its 2010 guidelines for antiretroviral

therapy for HIV in infants and children, WHO recommends d4T as one of the possible NRTIs to be given with 3TC and either an NNRTI or a PI in the first-line.²²

Because of the long-term risks of toxicity, particularly lipoatrophy 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.

The paediatric formulation of d4T is not adapted for resource-limited settings as it is supplied as a powder that requires reconstitution with clean, safe water, and once reconstituted, must be refrigerated.

Generic manufacturers have however been developing both double and triple fixed-dose combinations including d4T. As of May 2011, four d4T-containing FDCs for paediatric use were quality-assured by either US FDA or WHO prequalification.