

LAMIVUDINE/STAVUDINE/ NEVIRAPINE (3TC/d4T/NVP)

GENERAL INFORMATION

- Therapeutic class: Two NRTI and one NNRTI in a triple fixed-dose combination.
- 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
- Originator company and product brand name: No originator product exists.
- First approval by U.S. Food and Drug Administration (FDA): Not applicable.
- WHO Model List of Essential Medicines (EML): Included in the 17th edition – only the d4T 30mg presentation.²⁴ 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
- Patents: Individual patents on lamivudine (3TC), stavudine (d4T) or nevirapine (NVP) also affect this combination. Cipla first developed the FDC and applied for patents in several African countries.

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	Cipla (CF)	Hetero (CF)	Ranbaxy (CF)	Strides	Varichem
Who can access this price?		See annex 2				
3TC/d4T/NVP 30/6/50mg dispersible tablet	4	55 (0.038)				
3TC/d4T/NVP 60/12/100mg dispersible tablet	2	53 (0.072)				
3TC/d4T/NVP 150/30/200mg tablet	2	64 (0.088)	67 (0.092)	70 (0.096)	66 (0.090)	61 (0.083)

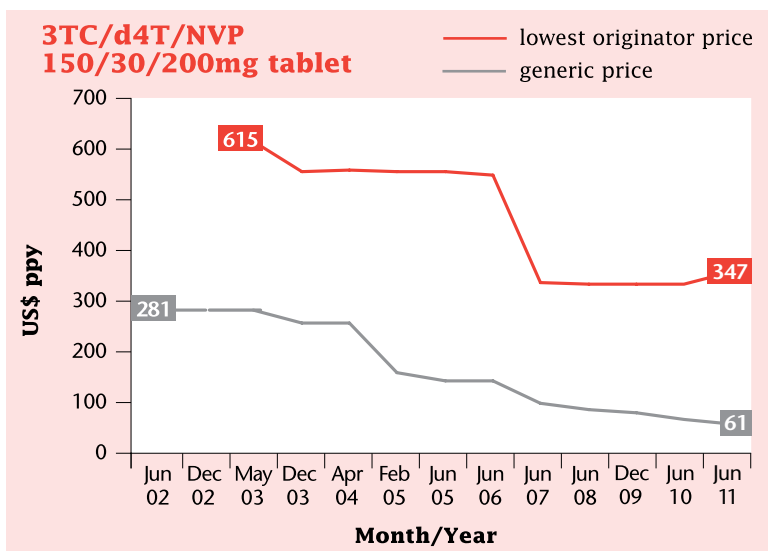
(CF) The Clinton Foundation has negotiated with this manufacturer for reduced prices on some formulations for countries in their consortium. See annex 13 for details.

Evolution of the lowest price quoted for developing countries since 2002:

As of May 2011, ten generic sources of 3TC/d4T/NVP 150/30/200mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

As there is no originator fixed-dose combination or co-pack, the price shown for the originator product is the sum of the three individual originator products.

Since 2002, the sum of the originator prices has decreased by 44%, while generic prices have dropped by 78%.



Continued overleaf

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 d4T-based regimens because of their long-term irreversible side effects and to move towards zidovudine- (AZT) or tenofovir-based (TDF) first-line regimens.⁷

For many years, the stavudine- (d4T) containing regimen 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.

It is time for countries to invest in a more robust, TDF-containing first-line regimen, such as TDF/3TC/EFV or TDF/FTC/EFV, which are both one pill, once a day or TDF/3TC + NVP (available in co-pack). While the price today is still higher than a d4T-based regimen, there is a need to generate greater demand which will, in turn, increase the competition and the economies of scale needed to further decrease prices.⁷

We can therefore expect to see a decrease in the use of this formulation in the future.

Patents

Cipla was able to develop this combination because none of the individual components were patented in India. Many generic manufacturers have followed suit in other developing countries, such as Thailand, where the medicines were not patented.

Extensive competition from numerous generic manufacturers has made this combination the most affordable triple ARV combination treatment to date.

Paediatrics

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends 3TC/d4T as one of the possible combinations to be given with 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.

However, together with AZT/3TC/NVP, 3TC/d4T/NVP is one of the two most commonly used first-line regimens for children today. 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, and therefore the 3TC/d4T double fixed-dose combination is 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.

The Paediatric Working Group at WHO has released clear guidance on the ideal strength of each of the individual ARVs in these fixed-dose combinations.

As of May 2011, two dispersible formulations were quality-assured by either US FDA or WHO prequalification.⁴³

HIV/TB co-infected young children cannot be given NVP because of interactions between NVP and TB drugs. As there is still no established dosing of EFV, the standard alternative to NVP, for children less than three years of age, there is an urgent need to establish the dosing of EFV for this age group.