

DIDANOSINE (ddl)

GENERAL INFORMATION

- Therapeutic class: Nucleoside reverse transcriptase inhibitor (NRTI).
- WHO guidelines: Indicated for second-line for children.²²
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Videx/Videx EC.
- First approval by U.S. Food and Drug Administration (FDA): October 1991 for chewable tablets; October 2000 for enteric-coated capsules.²³
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.²⁴
- World sales of originator product: 2005: US\$ 174 million; 2004: \$274 million; 2003: \$354 million. After 2005, there are no sales figures listed in the company's annual report.¹¹⁵
- Patents: The basic patent on ddl filed in 1985 by the National Institutes of Health (NIH), a U.S. government research institute, has expired, but BMS holds patents on improved formulations in some countries, which run until 2012 and 2018.¹⁰¹

PRICE INFORMATION

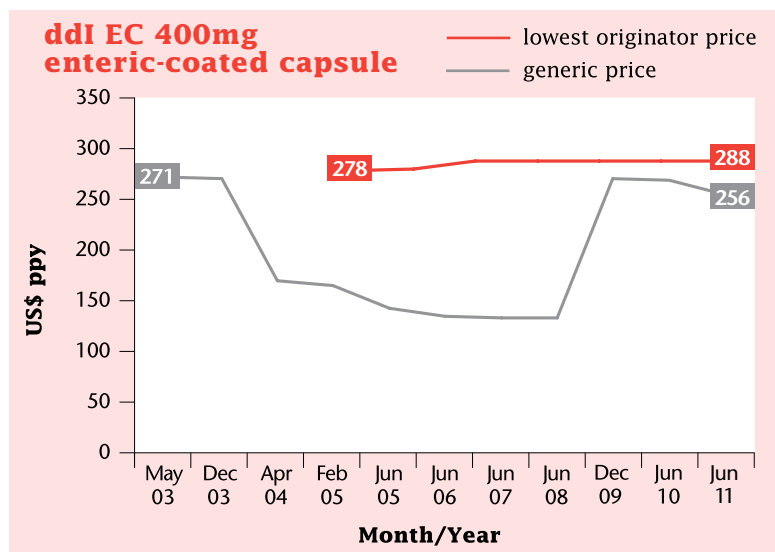
Developing country prices in US\$ per patient per year, as quoted by companies.

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

	Daily dose	BMS		Aurobindo	Cipla	Matrix	Ranbaxy
		Category 1 countries	Category 2 countries				
Who can access this price?		See annex 2 & annex 7		See annex 2			
ddl 2g powder for reconstitution (final concentration 10mg/ml)	12ml	276 (12.590/2g)					
ddl 25mg tablet	6	256 (0.117)			138 (0.063)		252 (0.115)
ddl 50mg tablet	-	(0.159)			(0.079)		(0.125)
ddl 100mg tablet	-	(0.213)		(0.133)	(0.129)		(0.166)
ddl 125mg enteric-coated capsule	1			110 (0.300)		119 (0.325)	
ddl 150mg tablet	-			(0.225)	(0.167)		
ddl 200mg tablet	-			(0.267)	(0.257)		
ddl 200mg enteric-coated capsule	-			(0.383)		(0.489)	
ddl 250mg enteric-coated capsule	1	223 (0.612)	316 (0.866)	170 (0.467)	103 (0.283)	172 (0.471)	134 (0.367)
ddl 400mg enteric-coated capsule	1	288 (0.789)	408 (1.118)	256 (0.700)	132 (0.363)	268 (0.733)	183 (0.500)

Continued overleaf ❖

Didanosine (ddl) continued



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

As of May 2011, three generic sources of ddl 400mg enteric-coated capsule were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

The first generic source of ddl 400mg enteric-coated capsule was quality-assured by WHO prequalification in June 2008 – 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 which explains the price increase.

SPOTLIGHT ON ACCESS ISSUES

In 2010, WHO released new recommendations for antiretroviral therapy for HIV in adults and adolescents. For second-line treatment, protease inhibitors such as ritonavir-boosted atazanavir (ATV/r) or lopinavir (LPV/r), and simplified NRTI options are recommended. Didanosine (ddl) (along with abacavir (ABC)) is therefore no longer recommended as one of the NRTI backbones in second-line therapy.⁷

Bristol-Myers Squibb (BMS)'s differential pricing structure limits the prices quoted in this publication to sub-Saharan Africa and low-income countries only. Some wealthy countries pay more than \$4,100 per patient per year for ddl 400mg enteric-coated (EC) capsules, a price which is prohibitive for many developing countries.¹⁰²

The enteric-coated capsules are better suited as they can be taken once daily and, unlike the tablets, do not contain a buffer. The buffer has been associated with stomach upsets and a bitter and chalky taste. In 2006, BMS discontinued the sale of the chewable/dispersible buffered tablets in the U.S. In December 2009, the company also discontinued the sale and manufacturing of ddl 200mg tablet globally due to low demand for the product.

In some African countries including Ethiopia, Ghana, Kenya, Nigeria, Tanzania and Uganda, BMS discontinued all commercial activities by the end of 2009, including

deregistration of all BMS products. BMS also discontinued the marketing of didanosine products in South Africa in December 2010.¹⁰⁶

Patents

No application claiming a patent on enteric-coated capsules has been published in India, allowing a generic version to be launched. However, where the patent has been granted in other developing countries, as in Brazil, China, and in ARIPO and OAPI countries, the importation of the more affordable version from India is blocked.

In Brazil, the active ingredient is in the public domain, which has allowed the government to produce locally the generic version as a powder for oral solution.¹⁰⁷ However, the enteric-coated capsule remains under patent protection.

Paediatrics

In October 1991, ddl was approved for use in children between two weeks and 18 years old.¹⁰⁸

In its 2010 guidelines for antiretroviral therapy for HIV in infants and children, WHO recommends ddl be given as part of second-line regimens, depending on what has been used as a first-line.²²

Paediatric formulations are available. For younger children, however, the only options are buffered tablets that come with a high pill burden, or the ddl powder for reconstitution, which requires multiple dilutions, first with

water and then with an antacid, to obtain the final concentration. Once reconstituted, the solution must be refrigerated and discarded after 30 days.

For older children who can swallow, the best-adapted option is the ddl EC 125mg capsule, but BMS offers no differential price for this product.

In 2007, BMS announced its intention to restructure the company, with plans to reduce the number of brands in the company's mature products portfolio by 60% and reduce the company's manufacturing facilities by more than 50% by 2011.¹⁰⁹ The BMS manufacturing plant in Meymac, France, was closed in June 2010. Fearing disruption in stocks for the developing world – and particularly for up to 7,000 paediatric patients in UNITAID-supported programmes¹⁰⁴ – due to lack of alternative quality-assured generic sources of ddl, civil society organisations¹⁰⁹ demanded that BMS address the foreseen shortage of didanosine 25mg and 50mg tablets ensuing from the plant closure.¹⁰⁴ The WHO also issued a memo warning developing countries of the impending shortage and recommended strategies to avoid treatment disruption including changing regimen.¹⁰⁵ BMS responded by fast-tracking the application for approval of the new plant with WHO prequalification programme by the end of 2010.

There is an urgent need for generic paediatric ddl 25mg tablets to be quality-assured by WHO prequalification.