

EFAVIRENZ (EFV)

GENERAL INFORMATION

- Therapeutic class: Non-nucleoside reverse transcriptase inhibitor (NNRTI).
- WHO guidelines: Indicated for first- and second-line for adults, adolescents and children.^{110,22}
- Originator company and product brand name: Bristol-Myers Squibb (BMS), Sustiva; or Merck, Stocrin.
- First approval by U.S. Food and Drug Administration (FDA): September 1998.²³
- WHO Model List of Essential Medicines (EML): Included in the 17th edition.²⁴
- World sales of originator product: 2010: US\$ 1.4 billion; 2009: \$1.2 billion; 2008: \$1.1 billion; 2007: \$956 million; 2006: \$791 million; 2005: \$680 million; 2004: \$621 million; and 2003: \$544 million.^{111, 112, 113, 114, 115, 116}
- Patents: The basic patent on EFV was filed in 1993 by Merck, and is due to expire in 2013.¹¹⁷ Subsequently, Merck filed for patent applications related to crystallized forms, due to expire in 2018.¹¹⁸

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/suspension dose or oral solution. Products included in the WHO List of Prequalified Medicinal Products (as of May 2011) are in **bold**.

	Daily dose	Merck	Aspen	Aurobindo (CF)	Cipla	Emcure	Hetero	Matrix (CF)	Micro Labs	Ranbaxy	Strides (CF)
Who can access this price?		See annex 2 & annex 10*	See annex 2								
EFV 30mg/ml oral solution	-	(0.094/ml)									
EFV 50mg capsule	-			(0.083)					(0.047)		
EFV 50mg tablet	-	(0.120)						(0.050)			
EFV 100mg capsule	-								(0.042)		
EFV 100mg tablet								(0.117)		(0.150)	
EFV 200mg capsule	3			116 (0.106)	134 (0.122)		152 (0.139)		80 (0.073)	97 (0.089)	
EFV 200mg tablet	3	394 (0.360)						183 (0.167)			113 (0.103)
EFV 600mg tablet	1	237 (0.650)	62 (0.170)	73 (0.200)	79 (0.217)	61 (0.167)	67 (0.183)	55 (0.150)	58 (0.158)	72 (0.197)	52 (0.143)

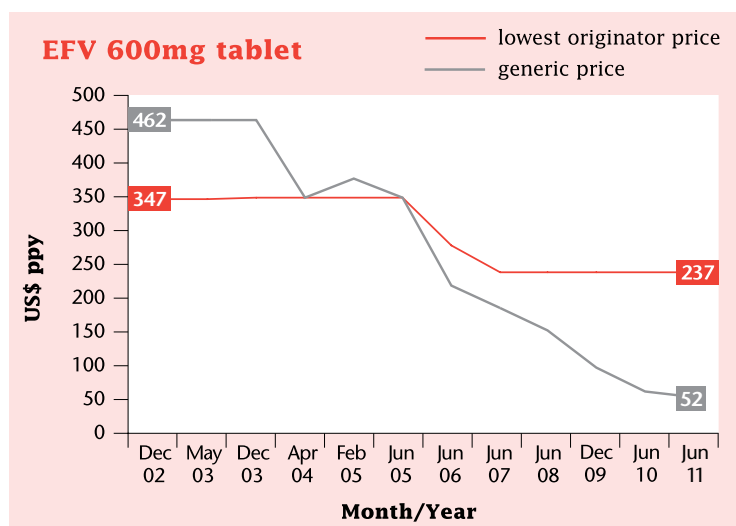
*For the first time this year, Merck decided not to give standardised price discounts to Category 2 countries. See 'Spotlight on access issues' below.

(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, seven generic sources of EFV 600mg tablet were quality-assured by US FDA or WHO prequalification. The one with the lowest price is shown here.

Since 2002, the originator price has decreased by 32%, while generic prices have dropped by 89%.



Continued overleaf ❖

SPOTLIGHT ON ACCESS ISSUES

Efavirenz (EFV) is a key drug for first-line treatment, as it is very potent, with once-daily dosing, and is well-tolerated.

In its new 2010 guidelines, WHO recommends the use of EFV – in combination with two NRTIs, one of which should be zidovudine (AZT) or tenofovir (TDF) – as a preferred first-line antiretroviral treatment.⁷

EFV is also recommended as the preferred NNRTI for patients starting ART while on tuberculosis treatment. Rifampicin, one of the main drugs used to treat TB, interacts with nevirapine (NVP), resulting in lower blood levels of NVP. EFV, however, does not have the same degree of interaction, and can be used as an alternative.

Merck has phased out the 200mg and 50mg capsule formulations, which have been replaced by tablets.

In 2011, Merck ceased offering standardised price discounts to all lower middle- and upper middle-income countries according to the World Bank Classification (see annex 6 for a list of these countries). The company proposes instead to negotiate discounted prices on a case-by case basis, based on country income and disease burden.

This is concerning for the affordability of products in middle-income countries, especially given that Merck's previous pricing strategy (published in previous editions of *Untangling the Web*) was to offer middle-income countries the EFV 600mg tablet at prices more than ten times more expensive than the generic version.

Patents

Merck does not hold a product patent for EFV in India. Generic competition from a number of Indian manufacturers has thus brought the price down significantly. However, a patent for the process of preparing form 1 of crystalline EFV was granted in June 2005.¹¹⁹ This process patent appears to protect a key process

for manufacturing EFV. This patent has therefore been opposed by Indian civil society organisations using the post-grant opposition procedures enshrined in India's patent law.¹²⁰

In addition, Gilead¹²¹ and BMS filed patent applications related to combinations of EFV with other ARVs. The patent office has already rejected Gilead's application,¹²² as combinations of known molecules are not patentable under India's patent law. BMS's efforts to receive a patent for the once-a-day pill EFV/FTC/TDF¹²³ could impact on access to improved first-line ARV treatment in the developing world and therefore warrants pre-grant patent opposition, particularly in India.

EFV remains expensive in countries where Merck holds patents that block the production and sale of generics. In countries where EFV is patented, governments and civil society groups have taken various measures to ensure generic competition and lower prices, including:

- In November 2006, Thailand issued a compulsory licence to import generic versions of EFV from India. As a result, the Thai government is now purchasing EFV at \$106 ppy, considerably lower than the previous price of \$511 ppy.^{124, 125}
- In May 2007, Brazil, after numerous unsuccessful negotiations with Merck, issued a compulsory licence to import more affordable generic versions of EFV from India. At the time, the price of EFV in Brazil was \$580 ppy and had not changed since 2003. After the compulsory licence, Brazil began to import a generic version prequalified by WHO for \$190 ppy. In February 2009, the public manufacturer Farmanguinhos (Fiocruz) launched the national generic version for use in the Brazilian health system.¹²⁶
- In South Africa, Merck's refusal to allow sufficient generic competition contributed significantly to the high price of the drug. This led the AIDS

Law Project, acting on behalf of the Treatment Action Campaign, to file a complaint before the Competition Commission in November 2007. As a result, Merck recently agreed to license its product to other producers, opening the opportunity for generic competition in South Africa, where six suppliers now market EFV or EFV-containing combination products.¹²⁷

Paediatrics

In 2010, WHO issued updated guidelines for antiretroviral use in paediatric HIV infection. These guidelines recommend that children under three be given two NRTIs plus nevirapine (to be replaced with lopinavir/ritonavir in case of peripartum nevirapin exposure); for children > 3 years the recommended regime is two NRTIs plus efavirenz (or lopinavir/ritonavir).

Although EFV was approved by US FDA for use in adults in 1998, there is still no established dosing of the medicine for children less than three years of age. There is an urgent need to establish the dosing of EFV for this age group, which is critical for children with HIV/TB co-infection.

In the absence of such data, treatment options for children remain limited, particularly for HIV/TB co-infected young children who cannot be given NVP because of interactions between NVP and TB drugs.

Paediatric formulations exist. In early 2008 however, BMS, which markets EFV in Europe, discontinued the manufacture of the 100mg capsule, further limiting options for paediatric patients.

The oral solution, while allowing more flexibility in dosing, must be discarded 30 days after opening, and is not interchangeable on a mg per mg basis with the solid dosage forms. The bioavailability of the oral solution is also less than 70% of the oral dosage forms, and hence a larger dose is required to obtain the same blood levels.