

Entecavir and Hepatitis B

Background on Hepatitis B

Hepatitis B virus (HBV) is highly endemic in South Africa and across sub-Saharan Africa, where around 8% of people are chronically infected, and rates of HBV-related liver cancer are some of the highest in the world. Globally, viral hepatitis causes approximately 1.3 million deaths every year—more than either malaria or tuberculosis—with around 240 million people chronically infected with HBV¹.

Risk groups

HBV can infect infants, children, teens and adults. This virus can be transmitted from mother to child, through sexual intercourse, unsterilised medical equipment and transfusion, and between children who may have open sores. Infection is more likely to become chronic, the younger infection occurs². Persons at risk for HBV infection may also be at risk of other blood borne infections, especially HIV and hepatitis C.

What are the treatment options for Hep B patients?

People with chronic hepatitis B who require treatment can be given oral antiviral agents, such as tenofovir and entecavir. Treatment with these drugs does not cure the infection, but keeps the virus under control. Some patients who are treated with interferon injections may clear the infection. Keeping the virus under control or clearing the infection reduces the risk of developing many of the complications of infection, like liver failure or liver cancer.

Where does entecavir fit into Hep B treatment?

Entecavir is the treatment of choice for hepatitis B for those with kidney impairment. Recommended dosage is 0.5 mg per day for patients who have not previously taken nucleosides, and 1mg per day for patients who have previously used lamivudine.³

How available is brand name entecavir in South Africa & how much does entecavir cost compared other countries?

Only the original manufacturer of entecavir, Bristol-Myers Squibb (BMS), is registered to market its product in South Africa. Entecavir is not procured by the National Dept. Of Health, and because of the high



"I CAN'T OFFER ENTECAVIR TO PATIENTS WITH HEPATITIS B & KIDNEY DISEASE—IT COSTS OVER R4700 PER MONTH. IF SOUTH AFRICA STOPS GRANTING NEW PATENTS ON ENTECAVIR, IT COULD ENABLE ACCESS TO MORE AFFORDABLE GENERICS."

– Dr. Monique Andersson
Tygerberg, Western Cape

SOUTH AFRICA PAYS THE PRICE
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price, is only available for public sector patients in special circumstances, following approval from a Pharmacy Committee. Medical aid schemes do not provide coverage for entecavir for cost reasons⁴, and HBV patients who need it must purchase the brand name drug through the private sector, which costs R4,775 or R5,500 per month, depending upon the dosage.

In India, by contrast, where generics are available through the private sector, the costs of treating a HBV patient with entecavir are much lower—the equivalent of around R400 or R650 per month for generic products, based on the dosage. Only Tamil Nadu state in India procures entecavir for the public sector from BMS, at the cost of approximately R1700

¹ Matthews PC, et al. Epidemiology and impact of HIV coinfection with Hepatitis B and Hepatitis C viruses in Sub-Saharan Africa. *J Clin Virol* (2014), <http://dx.doi.org/10.1016/j.jcv.2014.05.018>

² Ott JJ et al. Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine* 30 (2012) 2212-2219.

³ Bhattacharya D, Geffen D, Thio C. Review of Hepatitis B Therapeutics. *Clin Infect Dis*. 2010 Nov 15; 51 (10): 1201-1208

⁴ Telephone correspondence with Dr. Monique Andersson by MSF South Africa on October 3, 2014



per month⁵—overpaying substantially for the drug, given the lower cost of other available options in the country. A selection of price comparisons is provided in the chart below.

Further generic price reductions could be possible in the future, as the amount of active pharmaceutical ingredient required to produce entecavir tablets is very low, and the drug is coming off patent in many countries.

What would be the impact of having more affordable entecavir be available in South Africa?

Today, only a handful of patients in need are accessing entecavir in South Africa, while it is estimated that hundreds more would have a high chance of surviving if they were accessing the drug. Having better access to entecavir would enable clinicians to offer safe and effective therapy to all who need it in South Africa, and address one of sub-Saharan Africa’s major public health problems.

Manufacturer	ZAR Price per month* (0.5 mg tablet)		ZAR Price per month* (1 mg tablet)	
	South Africa	India	South Africa	India
Bristol-Myers Squibb	4,775	435	5,509	1,991
Cadila Healthcare	N/A	405	N/A	650
Cipla	N/A	405	N/A	758

*Price per month calculated based on the purchase price of 30 tablets. Indian private sector prices provided by Doctors Without Borders (MSF) India and converted from Indian rupees to South African rand on October 13, 2014. South African prices from September 19, 2014 database of the Medicines Price Registry (www.mpr.gov.za).

How do patents block access to generic entecavir?

The initial patent on entecavir expired in South Africa in 2011⁶, which should have permitted lower-cost generic competitors to enter the market. However, South Africa granted BMS three additional patents on entecavir that only expire between 2022 and 2026⁷. Two of these patents have lapsed—meaning BMS has not paid the renewal fees, and they cannot be enforced—while one patent covering a lower dosage form of entecavir remains in force. This patent is

currently under litigation in India⁸, but because it is in force in South Africa, generic suppliers may be discouraged from bringing their low-dose products to market.

A more recent patent on entecavir has not yet been received or processed by the Patents Office, but it could be filed up until the end of 2014.⁹ This patent covers the manufacturing process of entecavir, and is an example of patent evergreening—where companies file patents on minor changes to an existing drug to maintain patent protection and block competition. The same patent was recently overturned in the United States for failing to meet the criteria of inventive step.¹⁰ However, in South Africa, since no examination of patent applications occurs, if the patent is filed, it is likely to be granted to BMS. So long as BMS maintains a monopoly on entecavir in South Africa, the price is likely to remain high, and entecavir will remain out of reach for those who need it.

How can access to entecavir be improved in South Africa?

→ **Bristol-Myers Squibb** should lower the price of its entecavir product in South Africa.

→ **Generic manufacturers** should file registration dossiers in South Africa, for permission to bring more affordable entecavir products to market. This could facilitate the ability of the Department of Health to procure entecavir for the public sector.

→ **The Patents Office** should not reinstate lapsed patents on entecavir, and reject any new patents filed on entecavir.

→ **The Department of Trade and Industry** must finalise a national intellectual property policy and amend the country’s patent laws, in order to limit patent evergreening, and promote access to more affordable medicines.

⁵ Private correspondence between MSF Access Campaign in South Africa and India.

⁶ South Africa patent number: ZA 1991/07894. Current status available on: <http://patentsearch.cipc.co.za/>

⁷ South Africa patent numbers: ZA 2002/05900, ZA 2004/07672, ZA 2006/10141. Current status available on: <http://patentsearch.cipc.co.za/>

⁸ Basheer S. BMS Hepatitis Patent Invalidated: A Viral Effect for India? <http://spicyip.com/2013/02/bms-hepatitis-patent-invalidated-viral.html>

⁹ Patent number: WO/2013/177672. Current status available on patentscope.wipo.int

¹⁰ <http://www.marketwatch.com/story/teva-announces-us-court-of-appeals-upholds-ruling-confirming-invalidity-of-baraclude-patent-2014-06-12>

