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Will ViiV's Regulatory Stance Delay Access To Cabotegravir Despite MPP Deal?

Paxlovid Precedent A Concern

by Vibha Ravi

Scrip looks at the contours of MPP's recent sub-licensing deal for ViiV Healthcare's cabotegravir with Cipla, Aurobindo and Mylan, along with pricing dynamics and precedents to evaluate a few barriers to access

The Medicines Patent Pool (MPP) recently sublicensed *ViiV Healthcare*'s cabotegravir long-acting (LA) for HIV pre-exposure prophylaxis (PrEP) to *Aurobindo Pharma Limited*, *Cipla Limited* and *Viatris Inc.*' *Mylan Pharmaceuticals Inc.*, a move that will allow generic versions of the antiretroviral drug to be manufactured.

AIDS led to one death every minute in 2021, data from the joint United Nations Programme on HIV/AIDS (UNAIDS) show. "If current trends continue, we expect that, in 2025, we'll have 1.2 million people newly infected with HIV in that year. That's three times more than the 2025 target of 370,000," Mary Mahy, UNAIDS Director a.i. Data for Impact, has said.

While the number of people accessing PrEP doubled between 2020 and 2021, the cost of such preventive treatments is a deterrent. Making generic cabotegravir available via this deal in 90 countries where over 70% of all new HIV infections occurred in 2020 holds the potential to significantly reduce disease incidence and resultant death toll.

In July 2022, HIV specialist company ViiV Healthcare, owned by *GSK plc*, *Pfizer Inc.* and *Shionogi & Co. Ltd.*, had voluntarily licensed cabotegravir LA to the United Nations-backed organization. The non-exclusive sub-licenses from MPP have followed this March.

However, considering that access to COVID-19 drug Paxlovid - co-packaged nirmatrelvir/ritonavir - was delayed by fine print in the sub-licensing contracts, *Scrip* took a look

at the contours of the deal for cabotegravir, along with pricing dynamics and precedents to evaluate if there could be a slip between the cup and the lip.

What Are The Regulatory Requirements?

MPP had granted sublicenses for production of Pfizer's nirmatrelvir's active pharmaceutical ingredient (API) and finished product to 38 companies, including Indian manufacturers.

However, Pfizer had specified World Health Organization (WHO) prequalification or Stringent Regulatory Authorities (SRA) approval be secured for authorized generics. Hetero, the first to secure WHO prequalification, was able to do so a full eight months after it was eligible to sell Paxlovid in India via a local approval for restricted use under emergency situation.

In normal circumstances, a drug needs approval only from the domestic regulatory authority before being sold in a country. In India, the Drugs Controller General of India grants such authorization.

A Year Of Paxlovid - Where Is The Licensed Generic?

By Vibha Ravi

04 Jan 2023

It's been a year since Paxlovid was launched and The Medicines Patent Pool licensed Pfizer's nirmatrelvir. *Scrip* looks at a few likely reasons for authorized generics of Paxlovid not turning up and what lies ahead in 2023 as Hetero's version becomes the first with WHO Prequalification while two Chinese and a Korean company wait in the wings.

Read the full article here

The sub-licensing form for cabotegravir says the product has to be manufactured in a manner consistent with (i) Good Manufacturing Practice (GMP) and (ii) WHO pre-qualification standards or the standards of any SRA. Where such standards are not yet available, "temporary approval is to be sought through a WHO Expert Review Panel, as appropriate and if applicable."

All three companies granted a sub-license – Aurobindo, Cipla and Mylan - have GMP-compliant manufacturing facilities in India and Cipla also plans to make the product in South Africa. While the clause requiring GMP compliance shouldn't pose a hurdle, WHO pre-qualification or SRA approval could end up being a long-winded process.

Aurobindo has said it will manufacture the tablet and injectable dosage forms of the product at the APL Healthcare Unit IV, Naidupet and at the new Eugia sterile facility in Vizag. "The company has adequate capacities of world class standards, to meet the global demand for the product across the licensed territory" it added.

Considering a quality lapse for a PrEP product would have serious consequences, the regulatory

requirements for authorized generic versions of cabotegravir could be termed reasonable, but they are also likely to cause a delay in making the drug widely available. (Also see "*Amid US Cough Syrup Findings, Regulators Feel India Needs To Work On Perceptions But Also Make Improvements*" - Pink Sheet, 15 Mar, 2023.)

The Royalty Factor

Unlike sub-licensing deals for COVID-19 therapeutics like nirmatrelvir, *Gilead Sciences, Inc.*'s Veklury (remdesivir) and *Merck & Co., Inc.*'s Lagevrio (molnupiravir), where either royalty was zero or it was waived for the duration of the global public health emergency, royalty is to be paid on cabotegravir sales in a few countries.

Five percent of the net sales value of the licensed product will be charged for 10 out of 90 countries that the agreement covers. Notably this includes India where the three sub-licensees will make the drug, the others being Algeria, Egypt, Indonesia, Kyrgyz Republic, Morocco, Philippines, Tajikistan, Ukraine and Vietnam.

However, similar agreements have been signed by MPP for other life-saving drugs in the past. A voluntary licensing agreement with *Novartis AG* to increase access to nilotinib, a twice daily oral medication used to treat chronic myeloid leukaemia (CML), also envisages a 5% royalty payment. After all, originator companies do need to recover costs incurred on drug development. (Also see "*MPP Strikes Landmark Licensing Deal With Novartis On Nilotinib*" - Pink Sheet, 20 Oct, 2022.)

$144 Per Annum? The Cost-Benefit Dynamic

A study published in Lancet HIV to project the health benefits and risks of cabotegravir-PrEP introduction in settings in sub-Saharan Africa, assumed a base case cost of injectable cabotegravir-PrEP drug to be similar to oral PrEP.

This threw up a total annual cost of $144 ($114 per year and $264 per year considered in sensitivity analyses), a cost-effectiveness threshold of $500 per disability-adjusted life years averted, and a discount rate of 3% per year.

Its introduction was predicted to lead to a substantial increase in PrEP use with approximately 2.6% of the adult population (and 46% of those with a current indication for PrEP) receiving PrEP compared with 1.5% (28%) without cabotegravir-PrEP introduction across 20 years.

As a result, HIV incidence is expected to

MPP's Guide To Cutting Biosimilar Approval Times, Costs By Third Or More

By Vibha Ravi

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The Medicines Patent Pool has conducted a

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be lower by 29% (90% range across setting-scenarios 6–52%) across the same period compared with no introduction of cabotegravir-PrEP, it concluded.

Can Indian Companies "Just Do It"?

ViiV Healthcare had set the initial list price for cabotegravir LA at $3700 per dose in the US, where it was approved by the Food and Drug Administration (FDA) in December 2021 as Apretude for use in at-risk adults and adolescents weighing at least 35 kilograms (77 pounds) for PrEP.

study on the impact of licensing and technology transfer on the timeline and costs of developing five biosimilars, including Merck's Keytruda. While a licensing deal for pembrolizumab might not be a near-term possibility, the findings could help licensors, licensees and regulators increase access to medicines.

Read the full article here

"That's a lot of money; that's why that product cannot be used in low and middle-income countries" UNITAID spokesperson, Hervé Verhoosel, has said earlier.

If we go by the study quoted above, an annual cost of $144 per year is cost-effective, implying demand is sustainable at that price point. Considering the recommended dosage of first two injections administered four weeks apart, followed by an injection every eight weeks, annually seven doses would be needed in the first year and six doses thereafter.

That implies the drug would have to be sold at a price of $20.5-24 per dose. It's apparent the originator company can't offer such a steep discount given their R&D expenditure, existing cost structures and market dynamics.

Here's where Indian companies step in. Under the terms of the non-exclusive agreement, ViiV has offered technical knowhow to sub-licencees for the drug, a process that should help smooth manufacturing operations.

What's The Precedent?

As far as prices are concerned, Indian companies have gained the moniker 'Pharmacy To The World' on the strength of economically-priced generics and it seems possible to achieve the target price range calculated above.

Aurobindo has said it will develop the active pharmaceutical product (API) for cabotegravir in-house to "enable stronger control on supply chain and cost efficiencies."

The US government had paid $530 for each course of Paxlovid procured from Pfizer. However, Indian sub-licensees promised to deliver it in India at a fraction of that – Hetero deciding to price each course of its brand Nirmacom at below INR5,000 – which amounts to about $61.

Similarly, Merck & Co., Inc. agreed to supply molnupiravir to the US government at $700 each while Indian companies like *Dr. Reddy's Laboratories Ltd.* and *Mankind Pharma Ltd.* launched in India at about INR1,400 ($17) a course after MPP signed agreements with 27 generics manufacturers for its supply to 105 low- and-middle-income countries. (Also see "*Will Pfizer's Paxlovid Go The Lagevrio Way In India?*" - Scrip, 23 Mar, 2022.) (Also see "*Wave Of Molnupiravir Generics In India Amid Early Physician Cheer*" - Scrip, 29 Dec, 2021.)

Gilead Sciences, Inc. had faced a backlash when it priced remdesivir at $3, 120 per course for insured patients in the US despite the National Institutes of Health investing in its development. Licensing the drug at zero royalty to Indian manufacturers and giving them the freedom to determine the price they wanted to sell at helped dull some of the criticism later.

Hetero, first to launch in India, priced it at about $329 for a five-day course at INR5,400 per vial. The price kept going down with subsequent launches by more sub-licensees. Mylan launched at INR4,800 a vial, Cipla at INR 4,000 per vial, with *Zydus Lifesciences Limited* pulling out all stops when it launched at INR2,800 per vial. (Also see "*Zydus Cadila To Enter Remdesivir Fray In India By End-July*" - Scrip, 23 Jun, 2020.) (Also see "*Gilead Licensing Deal Expands Remdesivir Access, Capacity*" - Scrip, 13 May, 2020.)

MSF Hits Back At ViiV Over 'Infuriating' Cabotegravir Approach

By David Wallace

05 Apr 2023

In the wake of a licensing deal with the MPP that will see three generics firms produce versions of ViiV's long-acting cabotegravir for lower-income countries, Médecins Sans Frontières has urged the originator to be more transparent about plans to distribute the HIV prevention medicine in high-burden territories.

Read the full article here

It will be interesting to watch this space as the three chosen by MPP launch generic versions of cabotegravir, especially as the Médecins Sans Frontières/Doctors Without Borders (MSF) has said "despite repeated calls from civil society to increase CAB-LA's supply, ViiV's current global monopoly is unable to meet urgent global health needs."

It has also called on ViiV to "make information public on its global distribution plan" and "be transparent about the 'access price' in certain areas which differ dramatically from other regions."

ViiV Healthcare has regulatory approval for cabotegravir LA in the US, European Union, Australia, Zimbabwe, South Africa and Malawi.

The marketing authorization in Europe is for Vocabria (cabotegravir injection and tablets) in combination with *Janssen Pharmaceutical Cos.* of *Johnson & Johnson*'s Rekambys (rilpivirine injection) and Edurant (rilpivirine tablets) for treating HIV-1 infection. Meanwhile, the European Medicines Agency has validated the company's marketing authorization application to approve cabotegravir LA for PrEP.