Generic antiretrovirals in Europe: a blessing or a curse?

Ricardo Jorge Camacho
1 Molecular Biology Laboratory, Centro Hospitalar de Lisboa Ocidental
2 Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
Adults and children estimated to be living with HIV/AIDS

Total: 34 – 46 million
45 patients, intolerant to NNRTIs, receiving a Lopinavir/r generic drug as part of their first line regimen in South Africa

15 virologic failures (33.3%), with several PI drug resistance mutations
GLOBAL HEALTH

Bioavailability of Generic Ritonavir and Lopinavir/Ritonavir Tablet Products in a Dog Model

KEVIN W. GARREN, SIBTAIN RAHIM, KENNAN MARSH, JOHN B. MORRIS
Abbott Laboratories, 200 Abbott Park Road, Abbott Park, Illinois 60064

Received 4 November 2008; revised 8 January 2009; accepted 11 January 2009
Published online 19 February 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21712

• 5 generic formulations of Lopinavir/r
  LPV: 79% - 104,6%
  RTV: 89% - 102%

• 3 generic formulations of Ritonavir
  RTV: 96,6% - 101,2%
Patent expiration dates for antiretrovirals

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus
**Saquinavir - Key Patent, SPC, and Data Exclusivity Expiry (44 Country Coverage)**

**Date:** Dec, 2010  
**Price:** US$ 1,150.00  
**Publisher:** GenericswebPty Ltd.

<table>
<thead>
<tr>
<th>Applicant</th>
<th>Tradename</th>
<th>Generic Name</th>
<th>NDA</th>
<th>Approval Date</th>
<th>Type</th>
<th>RLD</th>
<th>Patent Number</th>
<th>Product</th>
<th>Substance</th>
<th>Delist Req.</th>
<th>Patent Expiration</th>
<th>Exclusivity Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bristol Myers Squibb</td>
<td>REYATAZ</td>
<td>atazanavir sulfate 021567</td>
<td>Jun 20, 2003</td>
<td>RX</td>
<td>No</td>
<td>&lt;disabled&gt;</td>
<td>&lt;disabled&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>REYATAZ</td>
<td>atazanavir sulfate 021567</td>
<td>Jun 20, 2003</td>
<td>RX</td>
<td>No</td>
<td>&lt;disabled&gt;</td>
<td>&lt;disabled&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>REYATAZ</td>
<td>atazanavir sulfate 021567</td>
<td>Jun 20, 2003</td>
<td>RX</td>
<td>No</td>
<td>&lt;disabled&gt;</td>
<td>&lt;disabled&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>REYATAZ</td>
<td>atazanavir sulfate 021567</td>
<td>Jun 20, 2003</td>
<td>RX</td>
<td>No</td>
<td>&lt;disabled&gt;</td>
<td>&lt;disabled&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bristol Myers Squibb</td>
<td>REYATAZ</td>
<td>atazanavir sulfate 021567</td>
<td>Jun 20, 2003</td>
<td>RX</td>
<td>No</td>
<td>5,849,911</td>
<td>Y</td>
<td>Y</td>
<td>&lt;disabled&gt;</td>
<td>&lt;disabled&gt;</td>
<td>&lt;disabled&gt;</td>
<td></td>
</tr>
</tbody>
</table>

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
## Patent Expiration Dates

<table>
<thead>
<tr>
<th>2005</th>
<th>2006</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Stavudine</td>
<td>Lamivudine</td>
<td>Nevirapine</td>
<td>Combivir</td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
<td>Indinavir</td>
<td>Efavirenz</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2014</th>
<th>2016</th>
<th>2018</th>
<th>2019</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Trizivir</td>
<td>Tenofovir</td>
<td>Kivexa (Epzicon)</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Lopinavir/r</td>
<td>Atripla</td>
<td>Fosamprenavir</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Truvada</td>
<td>Etravirine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td>Atazanavir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Blessing

Atripla: price per patient per year = US$12,480  (1 € = 1.3 US$)
Hospital Egas Moniz, Lisbon

- 2,000 HIV-1 and HIV-2 patients (~8% of all HIV infected patients in Portugal)

- 2010: 13,000,000 € on antiretrovirals

- 150 patients starting ARV therapy each year

- Spending estimate for 2015: 20,000,000 €
A Blessing? A Curse?

Atripla: price per patient per year = US$12,480  (1 € = 1.3 US$)
3TC vs FTC: selection of M184I/V

- TDF+3TC+EFV: 51% (178 pts)
- TDF+FTC+EFV: 24% (257 pts)
- TDF+3TC+PI/r: 22% (167 pts)
- TDF+FTC+PI/r: 11% (278 pts)

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus

A-G Marcelin et al, CROI 2011, abstract 617
Different Evolution of Genotypic Resistance Profiles to Emtricitabine Versus Lamivudine in Tenofovir-Containing Regimens

Valentina Svičer, PhD,* Claudia Alteri, PhD,* Anna Artese, PhD,† Federica Forbici, PhD,‡ Maria Mercedes Santoro, PhD,* Dominique Schols, PhD,§ Kristel Van Laethem, PhD,§ Stefano Alcaro, PhD,† Giosuè Costa,† Chiara Tommasi, MD,‡ Mauro Zaccarelli, MD,‡ Pasquale Narciso, MD,‡ Andrea Antinori, MD,‡ Francesca Ceccherini-Silberstein, PhD,* Jan Balzarini, MD, PhD,§ and Carlo Federico Perno, MD, PhD*‡

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus

\[ p = 0.01 \]

\[ p < 0.001 \]
We can expect an increase of resistance

- Is there an ‘acceptable’ level of resistance?
- Where will we draw the line between ‘acceptable’ and ‘unacceptable’ resistance?
- Can we accommodate it into guidelines?
- How will it affect resistance transmission?
## Patent Expiration Dates

<table>
<thead>
<tr>
<th>2005</th>
<th>2006</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine</td>
<td>Stavudine</td>
<td>Lamivudine</td>
<td>Nevirapine</td>
<td>Combivir</td>
</tr>
<tr>
<td>Didanosine</td>
<td></td>
<td></td>
<td>Indinavir</td>
<td>Efavirenz</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Saquinavir</td>
<td></td>
<td>Ritonavir</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2014</th>
<th>2016</th>
<th>2018</th>
<th>2019</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Trizivir</td>
<td>Tenofovir</td>
<td>Kivexa (Epzicom)</td>
<td>Raltegravir</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Lopinavir/r</td>
<td>Atripla</td>
<td>Fosamprenavir</td>
<td>Maraviroc</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Truvada</td>
<td></td>
<td>Etravirine</td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td>Atazanavir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
Gemini: Saquinavir/r vs Lopinavir/r

48 week, open-label, non-inferiority trial in drug-naïve patients

Boosted Saquinavir non-inferior to Lopinavir/r. Less Triglyceride elevations in Saquinavir/r arm
Saquinavir/r

- Virologic suppression rates < 70% at 48 weeks not acceptable anymore

- Saquinavir/r was not tested for non-inferiority and safety against Atazanavir/r and Darunavir/r

- Pill burden and adherence?
A return to BID regimens? Higher pill burden?

- There’s not a single randomized, prospective clinical trial proving superiority of BID vs OD regimens.

- Pill burden and adherence?

  An evidence-based review of treatment-related determinants of patients' nonadherence to HIV medications.
  Atkinson MJ, Petrozzino JJ.
  PRO-Spectus LLC, San Diego, California, USA. mjatkinson@ucsd.edu

- Less adherence when pill burden > 10 pills/day
## A curse: return to higher toxicities?

<table>
<thead>
<tr>
<th>Events, n</th>
<th>TDF+FTC+EFV (n = 526)</th>
<th>AZT+3TC+EFV (n = 519)</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total efficacy endpoints</td>
<td>95</td>
<td>98</td>
<td>0.95</td>
<td>.74</td>
</tr>
<tr>
<td>Confirmed virologic failure</td>
<td>78</td>
<td>78</td>
<td>0.99</td>
<td>.95</td>
</tr>
<tr>
<td>New AIDS event</td>
<td>11</td>
<td>12</td>
<td>0.89</td>
<td>.77</td>
</tr>
<tr>
<td>Death</td>
<td>18</td>
<td>20</td>
<td>0.99</td>
<td>.74</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Events, n</th>
<th>TDF+FTC+EFV</th>
<th>AZT-3TC-EFV</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total safety endpoints</td>
<td>243</td>
<td>313</td>
<td>0.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Initial dose modification</td>
<td>140</td>
<td>222</td>
<td>0.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 3-4 clinical events</td>
<td>115</td>
<td>116</td>
<td>0.96</td>
<td>.73</td>
</tr>
<tr>
<td>Grade 3-4 laboratory events</td>
<td>98</td>
<td>154</td>
<td>0.55</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus*
STARTMRK: Virologic and Immunologic Efficacy at Week 48

- Significantly shorter time to virologic response with RAL vs EFV ($P < .001$)
- Significantly greater CD4+ cell count increase with RAL vs EFV
  - $+189$ vs $+163$ cells/mm$^3$; $\Delta: 26$ cells/mm$^3$ ($95\%$ CI: 4-47)

STARTMRK: Lipid Changes From Baseline to Week 48

- Fewer patients initiated lipid-lowering therapy with RAL vs EFV (3 vs 11)
  - 4 patients in each arm increased lipid-lowering therapy
- Greater increases in all lipid parameters including HDL in EFV arm, no overall difference in TC:HDL ratio

Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus

So why isn’t Raltegravir making its way to first-line regimens?

- Because it’s BID?
- Because it’s not co-formulated with other drugs?
- Because it’s expensive?
- Because the toxicity of efavirenz is ‘acceptable’?
- How do we define ‘acceptable’ or ‘unacceptable’ toxicity?
Impact of generics for research and development of new HIV Drugs
Impact of generics for research and development of new HIV Drugs

- R&D costs are extremely high.

- Resistance is declining in Europe and USA. A reasonable return for development of new drugs can only be achieved if the drug makes its way to first-line or, at most, second-line therapy.

- With cheap generics like efavirenz or darunavir in the market, and residual multiresistance, is it worth to invest on new, expensive drugs?

- If the decision is not to invest, what will be the long term consequences for HIV infected patients?
You may ask questions, but probably I don't know the answers....
Incidence of within class resistance (WCR) and 'any' resistance over time


Presented at the 9th Eu. Workshop on HIV & Hepatitis – 25 – 27 March 2011, Paphos, Cyprus